

From Anxiety to Haemorrhage:
**Describing the Physiological Effects
that Confound the Prognostic
Inferences of Vital Signs in Injury**

Stevan R. Bruijns

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From Anxiety to Haemorrhage: **Describing the Physiological Effects that Confound the Prognostic Inferences of Vital Signs in Injury**

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Thesis Presented for the Degree of:

DOCTOR OF PHILOSOPHY (EMERGENCY MEDICINE)

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Declaration

I declare that this dissertation is my own unaided work. It is being submitted for the degree of Doctor of Philosophy (Emergency Medicine) to the Faculty of Health Sciences, University of Cape Town. It has not been submitted before for any degree or examination at any other university.

Signed by candidate

Stevan R. Bruijns

Signed this 15th day of July, 2013

University of Cape Town

For my wife Charmaine without whom this would not have been possible and my beautiful little girl, Megan, for putting up with daddy spending more time at the computer than he should

Abstract

Introduction

Many confounders affect vital signs' ability to accurately identify occult haemorrhage and outcome. The aim of this thesis was to establish the effect of spinal immobilisation, ambulance transport and anxiety on vital signs, and to develop better ways of using vital signs to identify trauma outcome.

Methods

Mixed methods were employed in five parts as follow: prospective, healthy volunteer, repeated-measures cohort to study the effect of spinal immobilisation on vital signs; retrospective case-control study (moderately-injured vs. uninjured) to evaluate the effect of anxiety on vital signs; retrospective chart-review of moderately-injured patients to study the effect of transport on vital signs; and two retrospective cohorts to evaluate the relationship between 48-hour outcome and respectively the difference between emergency department and prehospital vital signs, and novel markers derived from vital signs and age- including novel use of maximum heart rate (220 minus heart rate). Sample sizes were calculated for the prospective cohort and retrospective chart-review ($\alpha=0.05$), but not for the three retrospective studies which were drawn from large databases (Health survey for England and Trauma Audit and Research Network). Non-parametric statistics were used as sample data were not normally distributed.

Results

Spinal immobilisation was not associated with clinically relevant changes in vital signs. Moderately injured patients' heart rate was 10 beats per minute higher than that of the uninjured group, but none for blood pressure. No clinically relevant difference was found between transport and emergency department vital signs. Only a decrease in systolic blood pressure and increase in respiratory rate between prehospital and the emergency department (Δ) had significant (although weak) association with 48-hour outcome. Age was as good a predictor of 48-hour outcome as vital signs. Novel markers derived using combinations of age and vital signs were strongly, significantly associated with 48-hour outcome.

Discussion

The effect of immobilisation, anxiety and transport on vital signs is small and should not be considered as causes of vital sign derangements. Disappointingly the association between outcome and Δ vital signs was unconvincing. Novel markers incorporating age appear to be stronger predictors of outcome than using traditional vital signs.

Table of Contents

Abstract	5
List of Tables	10
List of Figures.....	11
List of abbreviations	12
Chapter 1 Introduction	14
The true value of traditional vital signs in trauma.....	14
<i>Tachycardia, hypotension, tachypnoea</i>	<i>16</i>
The pathophysiology of the cardiovascular response to trauma	18
<i>The triphasic response to haemorrhage</i>	<i>19</i>
<i>The response to tissue injury.....</i>	<i>20</i>
<i>The response to haemorrhage and tissue injury.....</i>	<i>21</i>
Non-haemorrhagic, non-injury causes of altered vital signs in trauma.....	21
<i>The effect of immobilisation, discomfort and pain</i>	<i>21</i>
<i>The effect of anxiety.....</i>	<i>22</i>
<i>The effect of transport</i>	<i>22</i>
Other important considerations in early trauma care.....	24
<i>The effect of pre-existing medical conditions (PMCs).....</i>	<i>24</i>
<i>The effect of old age</i>	<i>25</i>
Improving the clinical value of vital signs	25
<i>Improving vital signs in combination with other vital signs and/ or age.....</i>	<i>25</i>
<i>Trend between the prehospital and ED vital signs.....</i>	<i>26</i>
Aim	27
Objectives	27
Reporting structure.....	27
Chapter 2 Spinal immobilisation and vital signs	29
Declaration of author.....	29
Declaration by co-authors.....	29
Main findings	31
Argument for conducting study.....	31
<i>Aim</i>	<i>32</i>

<i>Objectives</i>	32
Copy of published paper	33
Discussion of study	38
<i>Methods</i>	38
<i>Results</i>	41
<i>Limitations</i>	46
<i>Chapter conclusion</i>	47
 Chapter 3 The difference between vital signs associated with minor to moderate injury and healthy subjects	48
Declaration of author.....	48
Declaration by co-authors.....	49
Main findings	50
Argument for conducting study.....	50
<i>Aim</i>	50
<i>Objectives</i>	51
Copy of published paper	52
Discussion of study	57
<i>Methods</i>	57
<i>Results</i>	60
<i>Limitations</i>	63
<i>Chapter conclusion</i>	64
 Chapter 4 Ambulance transport and vital signs	65
Declaration of author.....	65
Declaration by co-authors.....	65
Main findings	67
Argument for conducting study.....	67
<i>Aim</i>	68
<i>Objectives</i>	68
Copy of published paper	69
Discussion of study	72
<i>Methods</i>	72
<i>Results</i>	74

<i>Limitations</i>	75
<i>Chapter conclusion</i>	76

Chapter 5 The difference between emergency department and pre-hospital vital signs as indicators of mortality 77

Declaration of author.....	77
Declaration by co-authors.....	78
Main findings	79
Argument for conducting study.....	79
<i>Aim</i>	80
<i>Objectives</i>	80
Copy of published paper	81
Discussion of study	85
<i>Methods</i>	85
<i>Results</i>	90
<i>Limitations</i>	92
<i>Chapter conclusion</i>	92

Chapter 6 Vital signs, shock index and age-based markers as indicators of mortality..... 94

Declaration of author.....	94
Declaration by co-authors.....	95
Main findings	96
Argument for conducting study.....	96
<i>Aim</i>	97
<i>Objectives</i>	97
Copy of published paper	99
Discussion of study	105
<i>Methods</i>	105
<i>Results</i>	108
<i>Limitations</i>	110
<i>Chapter conclusion</i>	111

Chapter 7 Conclusion	112
An evaluation of the physiological effects of conditions that could potentially have an effect on vital signs	112
<i>Effect of immobilisation</i>	<i>112</i>
<i>Effect of anxiety</i>	<i>113</i>
<i>Effect of transport</i>	<i>114</i>
Novel ways of interpreting vital signs.....	115
<i>The value of deteriorating vital signs.....</i>	<i>115</i>
<i>The value of combining vital signs with age or other vital signs</i>	<i>115</i>
Further research	116
 References	 119
Appendices	132
Appendix A: Patient information sheet	132
Appendix B: Patient consent form	134

List of Tables

Table 1 Classification of shock based on estimated fluid and blood losses as taught by the Advanced Trauma Life Support (ATLS) course ⁴	15
Table 2 ATLS haemorrhagic shock classification guidance shows poor correlation of expected vital signs when compared with actual associated vital signs (ATLS guidance in bold)	17
Table 3 Triphasic response to haemorrhage	20
Table 4 Main findings of papers describing the effect of transport on vital signs	23
Table 5 Definitions relating to the course of pain ¹¹⁸	31
Table 6 Outcome measures, largest mean difference and standard deviation	41
Table 7 Comparing different data sets using mean z-scores (95% CIs)	43
Table 8 Effect sizes for variables at rest compared with variables fully immobilised	44
Table 9 Additional descriptive statistics (reference value in bold)	45
Table 10 AIS codes	58
Table 11 Descriptive statistics of injury/ age two-way analysis for heart rate (BPM)	60
Table 12 Descriptive statistics of injury/ age two-way analysis for systolic blood pressure (mmHg)	61
Table 13 Descriptive statistics of immobilisation/ age two-way analysis for systolic blood pressure (mmHg)	62
Table 14 Typical data transformations	86
Table 15 The two by two table	88
Table 16 Negative likelihood ratios at cut points nearest to 95% specificity	90
Table 17 Calculation of markers evaluated in study	97

Table 18 Specificity, sensitivity and positive likelihood ratios for ISS 9-15 subgroup using marker thresholds derived from 95% specificity for the full sample.....	109
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List of Figures

Figure 1 Comparing data sets using z-scores (95% confidence interval lines displayed for mean HR, SBP, RR, pain and discomfort VAS for each of the study phases	42
Figure 2 Diagrammatic description of two-way ANOVA; only one test variable (heart rate or systolic blood pressure) and one factor one variable (injury or immobilisation) were used per analysis	59
Figure 3 Example of a receiver operator characteristic curve.....	88
Figure 4 Fagan nomogram	89
Figure 5 Proportion of subjects that died within 48 hours according to age less, and greater than 55 years per ISS group	108

List of abbreviations

Δ , delta	HSE , Health Survey for England
ACS , acute coronary syndrome	ISS , injury severity score
AIS , Abbreviated Injury Scale	IQR , interquartile range
ANOVA , analysis of variance	JRCALC , Joint Royal Colleges Ambulance Liaison Committee
ATLS , Advanced trauma Life Support	km/h , kilometres per hour
AUROC , area under receiver operator characteristic curve	LR , likelihood ratio
BP , blood pressure	mmHg , millimetres mercury
BPAI , Pressure-age index	MP , minpulse
BPM , beats per minute	NHS , National Health Service
bpm , breaths per minute	PMC , pre-existing medical conditions
CI , confidence interval	PMI , pulse-max index
CNS , central nervous system	PTSD , post-traumatic stress disorder
CO₂ , carbon dioxide	RCT , randomised control trial
CT , computed tomogram	ROC , receiver operator characteristic curve
ED , emergency department	ROPE , heart rate-over-pressure-evaluation
FAST , focussed assessment with sonography in trauma	RR , respiratory rate
GCS , Glasgow coma scale	SBP , systolic blood pressure
HR , heart rate	SD , standard deviation

SI, shock index

SIA, shock index times age

SNS, sympathetic nervous system

TARN, Trauma Audit and research
Network

TRISS, Trauma and Injury Severity Score

UK, United Kingdom

USA, United States of America

VAS, visual acuity scale

WCE, white coat effect

University of Cape Town

Chapter 1

Introduction

Haemorrhagic shock as a result of trauma is a major cause of preventable death worldwide.¹⁻³ Early intervention is considered vital to avoid mortality and curb morbidity.⁴ Evaluation of the degree of physiological disturbance and, in particular, the volume of blood loss together with the mechanism of injury and anticipated anatomical injuries are considered essential information for delivering appropriate initial care.⁴⁻⁶ Evaluating the volume of blood loss is difficult and has traditionally been done by interpreting the traditional vital signs of heart rate (HR), blood pressure (BP), respiratory rate (RR) and level of consciousness. Unfortunately vital signs can be misleading, with the clinician being lulled into a false sense of security when these do not suggest a concern.⁶ Finding ways to identify occult haemorrhage and a risk of a poor outcome more reliably and earlier is an important step in reducing the mortality and morbidity associated with trauma.

The true value of traditional vital signs in trauma

A lot of value is placed on the use of traditional vital signs during the care of the acutely injured patient.⁴⁻⁶ Established thinking teaches that following injury and without appropriate treatment, significant acute blood loss will lead to reduced tissue oxygenation as a result of diminished organ perfusion; a condition which we refer to as haemorrhagic shock.⁷ Since the degree of tissue perfusion is difficult to measure it is generally taught that the traditional vital signs, heart rate, blood pressure and respiratory rate can be used as a proxy for reduced cardiac output (**Table 1**).⁴ Therefore traditional vital signs are used to guide trauma team activation criteria, thus dictating the level of institutional response readied in anticipation of the injured patient's arrival.^{5,6,8}

However, several authors have noted that vital signs do not adequately predict haemodynamically significant injuries, haemorrhage, or mortality.^{3,8-16} The reason for this is simply because the commonly taught association between hypovolaemia and hypotension/tachycardia is too basic: even if haemorrhage always caused abnormal vital signs, the presence of abnormal vital signs will not always be due to haemorrhage.^{2,3} Injuries such as head injury causing raised intracranial pressure, spinal cord and chest injuries, mechanism of trauma, ambient temperature and time from injury can further influence vital signs, but so might other non-injury related factors such as age, anxiety, pain, pre-existing medical

conditions, prescribed and non-prescribed medications.^{4,17-27} In fact, some of these turn out to be better prognostic indicators in the context of trauma than the vital signs which takes a supportive rather than a leading role.^{26,27}

Table 1 Classification of shock based on estimated fluid and blood losses as taught by the Advanced Trauma Life Support (ATLS) course⁴

Class of shock	Class I	Class II	Class III	Class IV
Blood loss (%blood volume)	≤15%	15%-30%	30%-40%	>40%
Estimated blood loss (ml)	≤ 750	750-1500	1500 - 2000	>2000
Heart rate (BPM)	<100	>100	>120	>140
Blood Pressure (mmHg)	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or Increased	Decreased	Decreased	Decreased
Respiratory rate (bpm)	14-20	20-30	30-40	>35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

ml, millilitre; BPM, beats per minute; bpm, breaths per minute

Despite conventional teaching, such as the Advanced Trauma Life Support (ATLS) course which has been taught as the *gold standard* of trauma care since 1978,^{4,28} clinicians as far back as the First World War have noted that injury and haemorrhage are not always associated with hypotension and/ or tachycardia.^{3,29-31} Back then it was documented that injured patients presented with either hypertension or hypotension, with very few presenting as normotensive.³¹ It was further observed that a significant amount of haemorrhage could be associated with little observable hypotension.³⁰ During the Second World War, in a study of 100 air-raid injured patients classified as “shocked”, 9% of patients

were found to be hypertensive at initial assessment, 28% normotensive and 63% hypotensive (defined as a systolic BP of less than 100mmHg).³²⁰ Of the hypotensive group only 43% had a HR greater than 100 beats per minute (BPM) meaning that only 27% of the patients presented with classic hypotension/ tachycardia.³² It is unclear exactly how *shock* was defined although it presumably included severe injuries, a poor outcome and softer signs such as pallor. Other reviews of wartime injuries found that despite acute compromise, HR was observed in some cases to remain below 60BPM.³³ The value of tachycardia, hypotension or tachypnoea for that matter has understandably been brought into question as predictors of acute haemorrhage.

Tachycardia, hypotension, tachypnoea

The problem with traditional vital signs is that when we use them to describe what is abnormal in trauma, we are in reality referencing thresholds based on observations noted over the last century. The variability of these measures in trauma is such that values on either side of these thresholds appear to be neither good predictors of outcome, nor reliable indicators of severity. Guly et al. cleverly made this point by showing that the commonly referenced *ATLS estimation of blood loss* guideline (**Table 1**) simply does not stand up to scrutiny.¹³ Using a large trauma database his group showed that despite patients having a tachycardia >100BPM, median SBP remained >110mmHg and respiratory rate (RR) <25 breaths per minute (bpm); despite patients having a SBP <100mmHg, median HR remained <95BPM with almost no change in RR; and despite patients having a RR >20bpm, median HR remained <105BPM and SBP >120mmHg (**Table 2**).¹³ Since a lot of value is placed on the use of traditional vital signs in early trauma care, it is therefore important to understand their strengths in aiding the trauma triage and resuscitation effort in context with their limitations to do so.

There is little merit in the use of HR in trauma. Although a tachycardia greater than 120BPM has a high specificity (around 95%), lower values tend to have poor accuracy for predicting either mortality or need for blood products; area under the receiver operator characteristic curve (AUROC), a measurement of accuracy, tends to be either non-significant or only just significant.⁹ As a result values under 120BPM do not rule out mortality or morbidity at all and can potentially falsely reassure an inexperienced clinician.^{9,2,34-37} The likely explanation for HR's poor form has to do with the relative bradycardia which is sometimes observed in relation to trauma (relative bradycardia is defined as a HR <90BPM with a SBP <90mmHg).^{9,37} Far from being an uncommon finding it

accounts for nearly a third of patients with a SBP <90mmHg according to the literature.^{9,35-37} In addition, relative bradycardia appears to occur despite objective measures of hypoperfusion (as demonstrated by base deficit <-5mmol/l and lactate >5mmol/l), independent of age, BP, injury severity or the presence of head injury.³⁸ Mortality rate tends to vary from higher to lower for patients with a relative bradycardia response to hypotension compared to those with a tachycardic response depending on the source referenced.^{9,12,34-37} It is therefore not surprising that HR is not included in physiological trauma scoring systems such as TRISS (Trauma and Injury Severity Score).

Table 2 ATLS haemorrhagic shock classification guidance shows poor correlation of expected vital signs when compared with actual associated vital signs (ATLS guidance in bold)

	Class 1	Class 2	Class 3	Class 4
Blood loss	<15%	15-30%	30-40%	>40%
ATLS HR guide (BPM)	<100	100-120	121-140	>140
Median SBP (mmHg)	136 (120-152)	138 (120-155)	133 (110-154)	130 (103-150)
Median RR (bpm)	18 (16-20)	20 (16-24)	22 (18-28)	24 (18-30)
ATLS BP guide (mmHg)	>100		<100	
Median HR (BPM)	83 (72-96)		88 (72-110)	
Median RR (bpm)	18 (16-21)		20 (16-24)	
ATLS RR guide (bpm)	14-20	21-30	31-40	>40
Median HR (BPM)	80 (72-92)	87 (75-100)	96 (80-112)	98 (80-118)
Median SBP (mmHg)	136 (120-151)	138 (120-155)	135 (118-154)	132 (112-150)

ATLS, Advanced Trauma Life Support; HR, heart rate; BPM, beats per minute; SBP, systolic blood pressure; RR, respiratory rate; bpm, breaths per minute

Although the general consensus is that a BP less than 90mmHg represents a threshold where poor outcome is more likely, it is interesting to note the variability and controversy around this value,^{10,11,39,40} particularly with regards to the elderly. Physiologically the elderly have higher blood pressures and a higher incidence of pre-existing medical conditions, including associated medications.^{25,41} Oyetunji eloquently suggested a change in dogma when considering the definition of hypotension in the elderly. His group showed that when in-hospital mortality is considered, a systolic BP (SBP) of less than 90mmHg suggested an appropriate level of concern for patients under 65 years, but that the threshold was 117mmHg for the over 65 years group.⁴² Although this was the first time

that the threshold for hypotension was redefined for the elderly, it is not the first time a redefinition had been suggested. Mostly the suggestion has been to redefine it to a threshold of 110mmHg, although this has been criticised by some as counter-productive with regards to modern hypotensive resuscitation teaching.^{39,40,43} Most of the scientific community concedes that despite suggesting a higher threshold, association between BP and mortality remains low; its AUROC is commonly described as below 0.6, or poor accuracy.⁴³ Given the significant level of mortality and morbidity (around a third of those that die and half of those with active haemorrhage will have a BP greater than 90mmHg); the only message from the literature is that there is no such thing as a normal BP in trauma.^{10,11,39,40}

As with HR and BP, there are many issues which affect the reliability of RR measurements. Most importantly, RR is the only traditional vital sign which is usually performed manually, in contrast with HR and BP which in general are measured electronically.⁴⁴ Many studies have shown that measurements (both manual and electronic) are not sensitive enough to rule out either bradypnoea or tachypnoea.⁴⁴⁻⁵⁰ In addition RR is, at least in part, under voluntary control (the only traditional vital sign that is) and since measurements are usually intrusive (even if done electronically), patients' RR could respond to both this and their injury.⁴⁴ Its association with hypotension is also in question with one study showing a non-significant odds ratio of 1.02 in predicting hypotension less than 90mmHg.¹² This finding suggests that the odds of having an abnormal RR associated with hypotension are no better than the odds of having a normal RR associated with hypotension. The inverse is also true with hypotension (variably defined in the literature as either less than 100mmHg or less than 90mmHg) showing a mean RR of around 19 to 22bpm.^{13,34,35} A higher RR does correlate with higher Injury Severity Score (ISS) although patients with high ISS (greater than 15) do not necessarily have an abnormal RR.¹³ Thus similar to HR and BP, RR seems to be useful only if it is abnormal, but not otherwise.

The pathophysiology of the cardiovascular response to trauma

Given the pathophysiological responses to trauma observed as far back as the First World War,^{3,29-31} it is not surprising that ample research already exists on the topic. What is important to understand, if the value of traditional vital signs is to be gauged, is that the response to trauma differs depending on whether the insult involves mainly haemorrhage, mainly tissue injury or a combination of the two.² These variations would be in addition to

any other factors that can also contribute to cardiovascular changes, such as described earlier.^{2-4,17-25}

The triphasic response to haemorrhage

The main research into the effect of haemorrhage on the cardiovascular system coincided with the launch of blood donor programmes during the Second World War.⁵¹ It was found that initially HR would increase along with peripheral vascular resistance, maintaining BP despite a drop in cardiac output. However, a sudden decrease in BP associated with a decrease in HR (relative bradycardia) ensued once around 1000ml of blood was donated. Often associated with syncope, it was also noted that systemic vascular resistance decreased during this phase. These effects could in most cases be reversed by infusing the donated blood back into the donor. Various studies have since confirmed these findings and several reviews have been published on the topic.⁵²⁻⁵⁸ The two main reflexes involved in this complex process include the arterial baroreceptor reflex and the depressor reflex, which relate to either a small amount of haemorrhage or a larger more critical volume respectively.

Following small volume haemorrhage (around 10- 15% of total blood volume), afferent activity from the arterial baroreceptors (in the aortic arch and carotid sinuses) decreases, intensifying sympathetic drive to the heart whilst lessening cardiac vagal activity.^{2,3,60,61} Concurrently peripheral vascular resistance increases as sympathetic vasoconstrictor tone rises, maintaining perfusion to vital organs (i.e. brain) at the expense to others that are less dependent on tissue oxygenation (i.e. skeletal muscle). (3) Vital signs show an increase in HR whilst BP is generally maintained.^{2,3}

Further blood loss (around 20% of total blood volume) leads to increased activity of the depressor reflex.^{2,3,62} It is still uncertain exactly how the afferent pathway works but it is likely that an underfilled ventricle (due to on-going haemorrhage) stimulates the cardiac vagal c-fibres.⁶³ Despite the fact that sectioning of these fibres reduces the relative bradycardia in experimental models,^{55,64,65} this does not account for the full effect seen.^{66,67} The efferent pathway on the other hand is through both the vagal and sympathetic vasoconstrictor nerves resulting in hypotension and a relative bradycardia.² It is known that efferent stimulation of this reflex is as a result of attenuation of the baroreflex activity described above, thus increasing vagal activity and reducing vascular tone.^{2,3,61} It can also be reversed by atropine, although this is not recommended as a treatment since it appears

to increase mortality.⁶⁷ Current thinking is that the bradycardia has a cardiac protective function by reducing cardiac workload when coronary blood flow would be compromised by low flow and tachycardia.⁶⁷

More recently it has become apparent that in addition to these two phases there is a third phase.^{2,56,69} An animal model showed that following a relative bradycardic phase, HR increases dramatically when around 44% of total blood volume is lost.⁵⁶ Similar findings were observed in a case series of 34 patients resuscitated for haemorrhagic shock.⁶⁹ Particularly of note was the association between improved survival and a relative bradycardia. Those with a bradycardia had around 34% total blood loss, whereas those that became tachycardic again had around 89% total blood loss and a greater mortality. In addition it was noted that those patients that had a relative bradycardia more readily responded to treatment than those whose heart rate had already started to rise.⁶⁹ The precise mechanism of how this third phase works is not quite clear yet.

Following on from this explanation it is interesting to note the discrepancies between **Table 1** (ATLS explanation) and **Table 3** (research based explanation).

Table 3 Triphasic response to haemorrhage

Phase	Reflex	Response
I (10-15% blood loss)	Arterial baroreceptor reflex suppressed	Tachycardia/ normo- to hypertension
II (20% blood loss)	Depressor reflex	Relative bradycardia/ hypotension
III (>44% blood loss)	Unknown	Tachycardia/ hypotension

The response to tissue injury

In contrast to the response to haemorrhage, tissue injury leads to an increase in BP and HR mediated through somatic and nociceptive fibres directly from the injury site which desensitises the baroreflex, increases sympathetic outflow and subsequently increases peripheral vascular resistance.^{2,3,70} Flow to vital organs (i.e. renal flow) is reduced in favour of skeletal muscle, a response similar to what is seen when the defence area of the brain is

stimulated.^{2,3,71} Although the full pathway is not completely established, it would appear that the body prepares for *fight or flight* when injury is concerned.⁷² Interestingly this response perpetuates and at 14 days post-injury is still partially present, resulting in a tachycardia post-injury which is not related to haemorrhage.^{3,73}

The response to haemorrhage and tissue injury

The cardiovascular response to haemorrhage is noticeably attenuated by the presence of injury. Essentially the tachycardia from the first phase of the triphasic model is reduced whilst the second phase bradycardia is counteracted, instead resulting in a tachycardia.^{3,55} Despite the pathophysiological responses to haemorrhage and tissue injury being quite different, when the two co-present, the response resembles the effect following tissue injury. What is most important is that mortality is higher when haemorrhage and injury co-presents than when haemorrhage presents on its own.⁷⁴⁻⁷⁶ This is despite the fact that the response following injury would instinctively appear better suited to protect against the hypotension seen in haemorrhage.⁵⁵ The reason for this apparent paradox has to do with the difference in reversibility of the two responses. As described earlier, the bradycardia phase associated with haemorrhage can in most instances be reversed through correcting the fluid balance,⁵¹ whereas with injury, the effect's recovery is delayed even after restoring fluid balance.⁷³ Given that this delayed effect includes diversion of flow from mainly the splanchnic circulation to skeletal muscle, it is postulated that the associated gut ischaemia contributes to the organ dysfunction (renal, liver, etc.) often seen in high severity trauma patients.⁷⁷

Non-haemorrhagic, non-injury causes of altered vital signs in trauma

The effect of immobilisation, discomfort and pain

As with tissue injury, pain attenuates the baroreceptors leading to an increase in sympathetic outflow.⁷⁸⁻⁸¹ Theoretically this should result in tachycardia, hypertension and tachypnoea. However, several studies have shown that a clinical effect is rarely observed.⁸²⁻⁸⁵ Although pain may occasionally cause vital sign changes, the lack of observed altered vitals in no way means that a patient is not in pain.

Spinal immobilisation is an important action during trauma resuscitation.^{4,5} According to ATLS this should be considered along with the airway during the primary survey.^{4,5} As a result, significant attention is given to protecting the spine both prehospital and in the emergency department (ED).^{4,5} In the prehospital stage various techniques and equipment

are used to ensure safe transfer to the ED.⁵ This is recognised as uncomfortable and painful. Studies so far have mainly been aimed at finding the most comfortable and least painful spinal immobilisation boards, harnesses and collars with no actual reference to their effect on vital signs.⁸⁶⁻⁹¹ These studies confirm that spinal immobilisation leads to increasing pain and discomfort and this appears to be accepted as a proxy for tissue ischaemia (mainly sacral and occipital pressure areas). Whether the resulting tissue injury along with the pain caused by immobilisation may be sufficient to elicit a clinical effect on vital signs remains unknown.

The effect of anxiety

Anxiety is currently understood to be regulated centrally, mainly through the amygdala nuclei which communicate with other central areas to affect respiratory rate, initiate an autonomic response and release stress hormones (such as cortisol and the catecholamines).^{18,19,92} The peripheral response leads to an increase in HR and BP through modulation of baroreflex sensitivity which appears to be independent of age, gender or baseline HR and BP.⁹²

In some patients, the HR and BP rise when they visit a doctor or other health provider. This is assumed to be due to anxiety and is known as the white coat effect (WCE).^{18,19} This has been demonstrated in both primary care and hospital settings.^{93,94} One post-traumatic stress disorder (PTSD) study has shown an increase in the resting HR (mean of 12BPM) for patients that were discharged within 12 hours from the ED with minor injury.⁹⁵ The BP was not measured in this study. Dedicated research into the WCE in a trauma setting, including its effect on vital signs already affected by injury or haemorrhage is unfortunately still lacking. Since injury and haemorrhage will also affect the baroreceptor sensitivity of an anxious casualty, it is simply not known which of these effects would dominate and if anxiety, as with pain, will have any effect at all given different levels of injury severity.

The effect of transport

Three studies have shown that vital signs are significantly affected by transport in healthy volunteers,^{20,22,96} Catecholamine outflow increased in healthy volunteers during different modes of transport (fast ambulance transfer versus slow transfer versus stair transport), with a clinical effect (relatively raised HR or BP from baseline) which was usually only notable in the most stressful transport mode (**Table 4**). A further study showed that the increase in catecholamine outflow could be diminished by pre-medicating volunteers with

midazolam. From these findings the authors concluded that transport anxiety has a measurable effect given high stress transport situations which may be deleterious for actual patients.⁹⁷

Table 4 Main findings of papers describing the effect of transport on vital signs

Author	Journal	Year	Size	Finding
Witzel (letter) ²²	Annals of Emergency Medicine	1999	54	Fifteen minutes slow transport (40km/h) significantly increased HR which returned to pre-transport values within 12 minutes; fast transport (70km/h) increased HR more significantly with no return to pre-transport value. In both models catecholamine levels were increased significantly.
Dörge ²⁰	Resuscitation	2001	32	Transport down three flights of stairs significantly increased HR, but ambulance transfer did not. In both models catecholamine levels were increased significantly.
Witzel ⁹⁶	Anaesthetist	2002	23	Helicopter transport increased HR and catecholamines significantly in association with subjective anxiety measurement.
Dörge ⁹⁷	Anesthesia & Analgesia	2002	72	As above (Dörge), but when midazolam was given pre-transport, catecholamine levels did not increase significantly.
Weber ²¹	Emergency Medicine Journal	2009	32	Transport of ACS patients caused an increase in catecholamines and subjective anxiety, but not HR or BP

km/h, kilometres per hour; HR, heart rate; BP, blood pressure; ACS, acute coronary syndrome

The lack of evaluating the effect of transport on vital signs in a real emergency is a limitation in all three of the healthy subject studies. A thorough search of the literature showed only one study that used subjects with an illness. Weber and colleagues showed

that in patients with acute coronary syndrome (ACS), despite a significant increase in catecholamine outflow, HR and BP remained unchanged during transport;²¹ with no control arm it was difficult to tell whether HR and BP were relatively higher than expected. Although an interesting finding, the main difference between this study and those that used healthy volunteers was that in this study catecholamine release showed no association with a subjective measurement of anxiety, whereas it did in the healthy volunteer studies.^{21,96} One explanation may be that when tissue injury is present (in this case caused by ACS), the effect of the injury or of anxiety relating to the injury already affecting the HR and BP, dominates and therefore the anxiety resulting from transport does not further add to this. No research has been done with regards to the effects of trauma and transport on vital signs. The effect of transport may vary in a trauma population depending on the level of injury severity. It is thus not yet known how vital signs are affected accordingly.

Other important considerations in early trauma care

The effect of pre-existing medical conditions (PMCs)

It is known that PMCs increase trauma mortality; and do so independent of age.^{25,98-101} From available research, the effect of PMCs on mortality appears to be strongest in minor to moderately injured, young to middle-aged patients, decreasing to nearly no effect for the most severely injured. The exact reason for this is not known but the currently accepted dogma is that it relates to diminished physiological reserve: essentially once a patient has suffered severe injury, the reduced physiological reserve caused by PMCs becomes less relevant than the injury itself and vice versa.⁹⁸ In addition, it has been observed that the risk of death in patients with a PMC was usually later (after 48 hours) and often not primarily due to the injuries.⁹⁹ Unsurprisingly, renal and cardiovascular disease appears to have the greatest effect.^{25,100} Both of these PMCs affect haemodynamics in some way or another: renal through hypertension and affecting fluid balance, cardiovascular through reduced cardiac output and both systems through commonly used drugs that affect chronotropy, inotropy, vasoactivity or the BP. Given that PMCs have little effect on severely injured patients and that the effect on less injured patients is mainly later, it can be argued that in early trauma care the presence of PMCs, although important, is less so than simply focussing on the presenting injury, especially if this is more severe.

The effect of old age

Given an aging population, geriatric trauma has increased more rapidly than any other patient group.¹⁰²⁻¹⁰⁴ The cause for injury in this population is largely due to a sustained active lifestyle, impaired cognitive and motor function, poor vision and hearing, and a higher prevalence of osteoporosis.¹⁰² Compared with a younger population, patients older than 65 years have nearly a two to three times higher mortality risk which is independent of ISS or PMCs.^{24,103,105-108} As a result geriatric patients are also more likely to be undertriaged (i.e. higher than expected mortality with mild to moderate ISSs) and less likely to have the trauma team activated (less concerning mechanism of injury, etc.).^{24,109} In addition, mortality trends towards later deaths (after 24 hours).^{103,105} Although 65 years is quoted above as a cut-off for defining geriatric trauma, there is by no means agreement in the literature with definitions ranging between 56 to 75 years.^{23,99,107,108} In the elderly injury severity seems to have very little to no relationship with either HR or BP.^{24,99} This has likely to do with the fact that elderly patients' HRs are less responsive to sympathetic stimulation and SBPs tend to be higher.^{2,41} Since vital signs and mechanism of injury are important triage criteria, at least where the elderly is concerned, better markers of severity is needed.

Improving the clinical value of vital signs

An important reason why vital signs are used in early trauma care is because of the relative ease with which they can be obtained at the patient's bedside, whilst the primary survey is being performed. Although continued use of markers with such low accuracy is untenable, any alternative considerations would first have to match their ease of use to be of any practical relevance in the acute setting.

Improving vital signs in combination with other vital signs and/ or age

Various attempts have been made to improve the predictive value of vital signs; in particular through combinations such as the shock index (SI; HR divided by SBP)¹¹⁰⁻¹¹² and the Heart Rate-over-pressure-evaluation (ROPE; HR divided by pulse pressure).¹¹³⁻¹¹⁴ Both these markers have performed better than traditional vital signs in identifying occult haemorrhage; SI in particular has also been shown to have utility in predicting injury severity, mortality and the need for massive transfusion.¹¹⁰⁻¹¹² The use of age to improve the utility of vital signs has only been shown in one paper so far. Zarzaur multiplied the SI with age to calculate the SIA. This showed much better association with 48 hour mortality

for those over 55 years than did vital signs or SI.²³ This work has not been reproduced or validated yet.

Another solution might be to consider the maximum HR as a proxy for physiological reserve. Maximum HR is used mainly in cardiology and sports medicine to describe the maximum HR at which the heart can still function without compromise. The accepted, most widely used calculation is 220 minus the age of the patient.^{115,116} Although this equation is not technically correct its result is close enough to give a reasonable indication of physiological reserve.^{115,116} It is also less complex than the true equation which is unlikely to be of practical use in the acute setting. The difference between markers using only vital signs and those that include age is that age remains constant for the duration of the acute treatment phase. The result is that for younger patients with better physiological reserves, younger age will have less of an effect than older age. Further research is needed to explore whether combinations of vital signs with other vital signs or age may provide an improvement in the accuracy of traditional vital signs alone.

Trend between the prehospital and ED vital signs

Vital signs that worsen between the initial measurements taken prehospital and in the ED might indicate a rapidly deteriorating patient and should be a source for concern at triage. Yet the size of the difference (also referred to as delta, Δ) for HR, SBP and RR has not yet been established. Only three papers were found that have directly or indirectly looked at Δ values. Arbabi et al. found that when the ED SBP is lower than the prehospital SBP, mortality increased by 27%.¹¹⁷ Along the same line, Franklin et al. found that mortality increased by 32% for patients that were normotensive in the field, but hypotensive in the ED.¹¹⁸ Neither study reported on either the Δ HR or Δ RR. One final study reported on the Δ SI.¹¹⁰ It found that a SI difference of greater than 0.3 resulted in a 28% mortality increase. If the traditional vitals are as unreliable as it would seem, then perhaps the trend between prehospital and ED may be a useful marker to direct an appropriate treatment response. Using Δ values would certainly be practical and would require no more information than is already available through simple, real-time, bedside measurements and those from the prehospital report. Once again further research is needed to evaluate this possibility.

Aim

The aim of this thesis was to establish the effect of spinal immobilisation, anxiety and ambulance transport on vital signs, and to develop better ways of identifying trauma mortality risk through the use of vital signs.

Objectives

1. To establish whether the pain and discomfort associated with spinal immobilisation and the manoeuvres commonly used in injured patients (e.g. log roll) affect the HR, BP and RR.
2. To compare the relationship between the HR and SBP respectively between immobilised and non-immobilised patients and the relationship between the HR, and SBP respectively in non-haemorrhagic, minimally injured patients and those of a non-injured control group.
3. To establish whether a difference exists between the HR, SBP and RR of patients with non-haemorrhagic traumatic injury, measured during ambulance transport and in the ED, with and without spinal immobilisation.
4. To evaluate whether the difference between SBP, HR, RR and SI taken in the ED and prehospital can predict outcome at 48 hours post admission following trauma.
5. To derive markers utilising age and maximum HR in combination with traditional vital signs and to evaluate and contrast these, along with the SI and SIA, with HR, SBP and RR in predicting 48 hour mortality.

Reporting structure

Each of the five objectives has been researched as individual studies and these are presented in the following five chapters. Each chapter includes a peer-reviewed publication that reports the methodology and pertinent findings from the individual studies. A foreword details the individual objectives for each study, its main findings as well as the argument for conducting the study and is followed by the publication in its published format. This is followed by a detailed discussion of the study, explaining the specific methods, reporting on further unpublished results and discussion of the study limitations. During the discussion, the findings in each chapter are linked to those of other chapters. Findings were reported in the publications using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.¹¹⁹ The STROBE statement is an

internationally supported framework for observational research conduct and reporting.

Chapter 7 brings the findings of all the individual studies together and presents these in terms of the overall thesis aim, thus concluding the thesis' findings in a single discussion.

Chapter 2

Spinal immobilisation and vital signs

Reference

Bruijns SR, Guly HR, Wallis LA. Effect of spinal immobilization on heart rate, blood pressure and respiratory rate. Prehosp Disaster Med. 2013;28(2):1-5

Declaration of author

In the case of Chapter 2, the nature and extent contribution to the work was the following:

- **Nature of contribution:** SRB and HRG came up with the original idea; SRB did the majority of planning, wrote the first and subsequent drafts of the proposal, collected the data, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript and this chapter and is the corresponding author and guarantor of the publication; HRG and LAW contributed to the proposal, manuscript and chapter.
- **Extent of contribution:** SRB: 85%; HRG: 10%; LAW: 5%

The following co-authors contributed to the work

1. Prof Lee A Wallis
2. Dr Henry R Guly



Signed: Stevan R Bruijns

Declaration by co-authors

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other author of the publication according these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from date indicated below

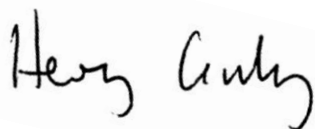
Location of stored data: Raw data are stored within a password protected database at Plymouth Hospitals NHS Trust, Plymouth, United Kingdom. Data collection sheets are securely kept in the study research folder which has been moved to the Research and Development Department of Derriford hospital following conclusion of the study.



Prof Lee A. Wallis

15 July 2013

Date



Dr Henry R. Guly

15 July 2013

Date

Main findings

- Spinal immobilisation does not appear to contribute significantly to changes in HR, BP or RR in healthy volunteers
- Abnormal vital signs in the trauma setting are unlikely to be caused by immobilisation

Argument for conducting study

Research has shown that spinal immobilisation causes pain or discomfort in pressure areas despite numerous advances in equipment to reduce this.⁸⁶⁻⁹⁰ As discussed in the introduction, acute pain in the ED does not generally cause any significant clinically observable changes in the HR, BP or RR. However, an important difference between traumatic pain and pain from immobilisation is that with traumatic pain, the most acute perception of pain is likely to be the period right around the outset, which then tapers off as bleeding, swelling and pressure reduces (phasic followed by tonic phase, **Table 5**). Whilst with spinal immobilisation pain, pain is expected to increase more linearly in relation to duration of immobilisation as pressure areas become more ischaemic (increasing tonic phase, no phasic phase). This is also discussed in the paper (part of table 4 from the original paper has been reproduced here as **Table 5**).¹²⁰ As such, it cannot simply be assumed that what applies to acute pain in the ED also applies to spinal immobilisation, hence the need for this paper. Any effect on vital signs shown would necessitate this to be taken into account during the evaluation of vital signs in a real immobilised trauma patient. This would likely render interpretation more complex and less intuitive. The expected outcome however, was that the null hypothesis (no difference) would be correct and that any changes if present would be of minor significance.

Table 5 Definitions relating to the course of pain¹¹⁸

Course of pain
<ul style="list-style-type: none">• Phasic pain: short duration, high intensity pain usually at the time tissue injury occurs Example: phlebotomy• Acute pain: includes the phasic component and then a tonic phase where pain resolves over hours to days Example: sprained ankle• Chronic pain: persists for longer than what is normally expected for healing and recovery Example: complex regional pain syndrome

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Aim

To establish whether the pain and discomfort associated with spinal immobilisation and the manoeuvres commonly used in injured patients (e.g. log roll) affect the HR, SBP and RR.

Objectives

1. To compare HR, SBP, RR, pain visual acuity scale (VAS) and discomfort VAS at rest (supine and without immobilisation) with the same variables respectively when full immobilisation (spinal board, rigid cervical spine collar and head blocks) has been applied
2. To compare HR, SBP, RR, pain VAS and discomfort VAS at rest (supine and without immobilisation) with the same variables respectively directly following a modified log roll
3. To compare HR, SBP, RR, pain VAS and discomfort VAS at rest (supine and without immobilisation) with the same variables respectively when partially immobilised (rigid cervical spine collar and head blocks)
4. To compare HR, SBP, RR, pain visual acuity scale (VAS) and discomfort VAS at rest (supine and without immobilisation) with the same variables respectively following removal of immobilisation, resting semi seated.

A copy of the published paper follows over the next five pages

Effect of Spinal Immobilization on Heart Rate, Blood Pressure and Respiratory Rate

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Conflicts of interest: none

Keywords: blood pressure; discomfort; heart rate; hemorrhage; pain; respiratory rate; spinal immobilization; trauma; vital signs

Abbreviations:

ATLS: Advanced Trauma Life Support
ED: Emergency Department
HR: Heart rate
RR: Respiratory rate
SNS: Sympathetic nervous system
SBP: Systolic blood pressure
VAS: Visual analog scale

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Abstract

Introduction: Vital signs remain important clinical indicators in the management of trauma. Tissue injury and ischemia cause tachycardia and hypertension, which are mediated via the sympathetic nervous system (SNS). Spinal immobilization is known to cause discomfort, and it is not known how this might influence the SNS and contribute to abnormal vital signs.

Hypothesis: This study aimed to establish whether the pain and discomfort associated with spinal immobilization and the maneuvers commonly used in injured patients (eg, log roll) affect the Heart rate (HR), Systolic Blood Pressure (SBP) and Respiratory rate (RR). The null hypothesis was that there are no effects.

Methods: A prospective, unblinded, repeated-measure study of 53 healthy subjects was used to test the null hypothesis. Heart rate, BP and RR were measured at rest (five minutes), after spinal immobilization (10 minutes), following log roll, with partial immobilization (10 minutes) and again at rest (five minutes). A visual analog scale (VAS) for both pain and discomfort were also collected at each stage. Results were statistically compared.

Results: Pain VAS increased significantly during spinal immobilization (3.8 mm, $P < .01$). Discomfort VAS increased significantly during spinal immobilization, after log roll and during partial immobilization (17.7 mm, 5.8 mm and 8.9 mm, respectively; $P < .001$). Vital signs however, showed no clinically relevant changes.

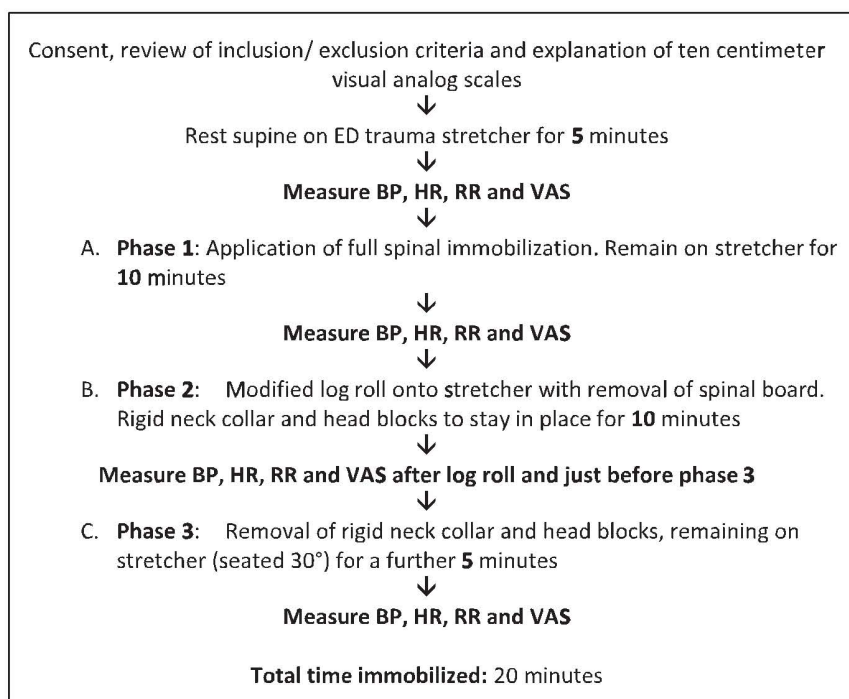
Discussion: Spinal immobilization does not cause a change in vital signs despite a significant increase in pain and discomfort. Since no relationship appears to exist between immobilization and abnormal vital signs, abnormal vital signs in a clinical situation should not be considered to be the result of immobilization. Likewise, pain and discomfort in immobilized patients should not be disregarded due to lack of changes in vital signs.

Bruijns S, Guly H, Wallis L. Effect of spinal immobilization on heart rate, blood pressure and respiratory rate. *Prehosp Disaster Med.* 2013;28(2):1-5.

Introduction

In the management of the trauma patient, vital signs are considered important clinical indicators for the clinician as evidenced by their inclusion in trauma team activation criteria, and much emphasis is placed on them in current trauma training.^{1,2} Despite evidence challenging the usefulness of vital signs in the trauma setting, their measurement still remains a core component of early trauma care, when little objective information (other than perhaps the visible injury or mechanism) is known.³

Both tissue injury and ischemia cause tachycardia and hypertension mediated via the sympathetic nervous system (SNS) in a manner similar to that of the fight-or-flight reaction.⁴ The response to tissue injury attenuates the cardiovascular response to hemorrhage through a reduction in sensitivity of the baroreceptor and depressor reflexes.⁴ The result is that relative cardiovascular stability is maintained longer; however, for clinicians this makes hemorrhage more difficult to diagnose when injury is present.⁴ Pain only attenuates the vagal component of the baroreceptor reflex, leaving the sympathetic component intact.⁵ Sympathetic nervous system activation may therefore result in measurable tachycardia, tachypnea, and hypertension, although these are not usually seen unless pain intensity and duration is sufficiently high.^{6,7} The exact details of this relationship remain unclear, but it is possible that sufficient pain may, like injury, obscure the cardiovascular response to hemorrhage,⁸ making clinical detection of its presence more difficult.



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Figure 1. Strategy Employed to Collect Data from Healthy Volunteers

Spine immobilization using a firm cervical collar, head restraints and a spinal board is advocated by the Advanced Trauma Life Support (ATLS) course material as a precaution against causing or worsening a spinal cord injury in an injured or potentially injured person.² This inevitably results in pain and discomfort.⁹⁻¹³ Kwan et al reviewed 17 randomized controlled trials (RCTs) in order to evaluate the effect of spinal immobilization on healthy subjects.⁹ Of these RCTs, four used pain and another four used discomfort as an outcome measure. All the studies showed that subjects reported a significant increase in pain or discomfort when immobilized.⁹ A thorough search of current literature databases (including the British Nursing Index, EMBASE, CINAHL, MEDLINE and Google Scholar) was undertaken, searching for papers that describe an association between vital signs and spinal immobilization. This search revealed five papers of varying quality, describing respiratory restriction associated with spinal immobilization using various devices, though none of these papers included comments on the respiratory rate (RR).^{9,14-17} No literature could be found describing the effect of spinal immobilization on heart rate (HR) or systolic blood pressure (SBP).

Given the paucity of literature, it is not known whether sustained pain and discomfort caused by spinal immobilization may be a sufficient stimulus to affect a patient's vital signs. If so, this effect will need to be taken into account during evaluation of vital signs in the injured, spinal immobilized patient, as immobilization may—like tissue injury—make detection of hemorrhage difficult. This study aimed to establish whether the pain and discomfort associated with spinal immobilization and the maneuvers commonly used in injured patients (eg, log roll) affect the HR, BP and RR. The null hypothesis was that there are no effects.

Methods

A prospective, unblinded, repeated-measure study was used to test the null hypothesis. To power the study to 80% ($\alpha = 0.05$), 52 subjects were required to reject the null hypothesis if the mean differences in HR, RR and SBP were 10 beats per minute, 2.5 breaths per minute and 7.5 mm Hg, respectively (a priori consensus among authors). Uninjured, healthy, adult volunteers were recruited from staff in Derriford Hospital's Emergency Department (ED) (Plymouth, UK) and from paramedic students at Plymouth University. Subjects were excluded from participation if they: (1) had known cardiovascular or respiratory disease; (2) were taking any medications known to affect the heart rate (eg, sympathomimetics or antihypertensive medication); (3) were pregnant; (4) suffered with back problems (including previous back surgery); or (5) developed a symptomatic bradycardia (pulse <60), tachycardia (pulse >120), hypotension (SBP <90) or any hypertension (SBP >180) before or during data collection. Informed consent was obtained from all participants. The study received ethical approval through the NHS South West 1 Research Ethics Committee (REC) (10/H0203/25) and University of Cape Town REC (014/2010).

Outcomes measured were the resting HR, BP, RR, pain VAS and discomfort VAS; these were compared with values 10 minutes after full spinal immobilization (Phase 1), following the log roll (Phase 2), 10 minutes after removal of spinal board (Phase 3), and final resting values. Clinically relevant outcome measures (a priori determined) were mean differences for HR, RR and SBP of ≥ 10 beats per minute, 2.5 breaths per minute and 7.5 mm Hg, respectively. The strategy employed for data collection is shown in Figure 1.

The first author collected all the data, and as subjects were uninjured, performed a modified log roll in Phase 2 of the study.

	Mean	Median	SD	Range		95% CI	
				Lower	Upper	Lower	Upper
Age	37	35	13	18	62	33.55	40.49
Age Males (n = 11)	35	36	10	20	51	28.41	41.59
Age females (n = 42)	38	35	13	18	62	33.41	41.69
SBP at rest (mmHg)	114	114	13	84	151	110.48	117.41
SBP fully immobilized	115	112	13	94	150	110.82	118.16
SBP after log roll	114	114	12	94	142	110.65	117.31
SBP partial immobilized	112	111	12	90	140	108.35	114.74
SBP semi seated	113	113	12	91	145	110.21	116.65
HR at rest (beats/min)	66	66	11	45	93	62.38	68.60
HR fully immobilized	64	62	10	46	83	61.10	66.37
HR after log roll	63	62	10	41	85	60.08	65.35
HR partial immobilized	62	64	10	45	88	59.76	65.10
HR semi seated	63	62	9	43	81	60.02	65.00
RR at rest (breaths/min)	14	14	4	8	22	13.01	14.99
RR fully immobilized	14	14	4	8	22	13.15	15.23
RR after log roll	14	14	4	8	24	13.13	15.36
RR partial immobilized	14	14	4	8	24	12.58	14.59
RR semi seated	13	14	3	8	20	12.41	14.16
Pain VAS at rest (mm)	0.35	0	2.45	0	18	-0.32	1.03
Pain VAS fully immobilized	3.81	0	9.36	0	42	1.23	6.39
Pain VAS after log roll	0.53	0	2.54	0	17	-0.17	1.23
Pain VAS partial immobilized	1.45	0	5.48	0	31	-0.06	2.96
Pain VAS semi seated	0.13	0	0.94	0	7	-0.13	0.39
Discomfort VAS at rest (mm)	0.53	0	2.90	0	21	-0.27	1.33
Discomfort VAS fully immobilized	17.68	15.07	17.37	0	75	12.89	22.47
Discomfort VAS after log roll	5.84	2.05	9.18	0	46	3.31	8.37
Discomfort VAS partial immobilized	8.90	2.05	17.32	0	89	4.13	13.68
Discomfort VAS semi seated	0.13	0	0.94	0	7	-0.13	0.39

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Table 1. Descriptive Statistics of Age and Data Sets (control group in bold)

Abbreviations: SBP, systolic blood pressure; SD, standard deviation; RR, respiratory rate; VAS, visual analog scale

Heart rate and SBP were obtained using the same manual, electronic sphygmomanometer for all subjects, and RR was manually counted over a minute. Full spinal immobilization consisted of a correctly-sized rigid neck collar, rigid spinal board and head blocks. Discomfort and pain were measured separately using a 100-point visual analog scale (VAS). An evaluation of discomfort also was made using a 100-point VAS. This scale has been used previously in spinal immobilization literature as a subjective measure of tissue ischemia.^{13,18}

Data were analyzed using SPSS Statistics version 19 (IBM, Armonk, New York USA). Mean, median, standard deviation (SD), range and 95% confidence intervals (CIs) were used to describe the data sets. Friedman's analysis of variance (ANOVA) was used to evaluate SBP, HR, RR, pain VAS and discomfort VAS. A Wilcoxon signed-rank test (with a Bonferroni correction to control for the family-wise error) was used for post-hoc testing for pain VAS and discomfort VAS.¹⁹ Effect size was determined using Pearson's correlation coefficient (r).¹⁹ The correlation coefficient (r) is a useful test, not only to measure strength of a relationship, but also to measure the strength of an experimental effect between two variables ($r = 0.10, 0.30$ and 0.50 denote small, medium and large effects respectively).¹⁹ Statistical tests

were two-sided and a $P < .05$ was deemed statistically significant (with the exception of the Bonferroni correction where $P < .01$ was used to indicate significance).¹⁹ Finally, data were transformed to z-scores to allow expression of values in SD units, thus allowing direct comparison among the vital signs, pain VAS and discomfort VAS data sets.¹⁹

Results

Data were collected from 53 subjects (11 male) and there were no missing data points.

Friedman's ANOVA for SBP, HR and RR showed statistically significant differences within their respective data sets ($P < .05, .01$ and $.01$ respectively), but when compared to outcome measures, these differences were not clinically relevant (Table 1). The pain and discomfort VAS also showed statistically significant differences within their respective data sets (Friedman's ANOVA, $P < .001$ for both). Outcome measures were not set for the pain and discomfort VAS; these were further evaluated using the Wilcoxon signed-rank test and effect size (r) measurement, where post-hoc analysis revealed a significant mean difference. The mean differences among discomfort at rest, discomfort with spinal immobilization, logroll, and partial immobilization

	Z	P	r
Pain VAS at rest compared to pain VAS:			
Full immobilization	-3.01	.003	-0.29 (small effect)
Discomfort VAS at rest compared to discomfort VAS:			
Full immobilization	-5.97	<.001	-0.58 (large effect)
After log roll	-4.08	<.001	-0.40 (moderate effect)
Partial immobilized	-4.32	<.001	-0.42 (moderate effect)

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Table 2. Significant Findings When *At Rest* Control Group Mean Compared to Other Group Means

significant ($P < .001$ each) and effect sizes were -0.58 , -0.4 and -0.42 respectively (Table 2). The mean difference between pain at rest and pain with spinal immobilization was the only significant finding on post-hoc analysis ($P = .003$) although the effect was small (0.13).

Figure 2 (supplementary file online) gives a graphical interpretation of the data sets using z-scores (values can be found in Table 4, supplementary file online). These show the significant variation (95% error bars) in the discomfort VAS despite insignificant changes in SBP, HR and RR.

Discussion

This study is the first in a series of studies to evaluate the physiological effects that confound the prognostic inferences of vital signs in injury. Despite a significant increase in discomfort (moderate to high effect) and pain (small effect), the volunteers' SBP, HR and RR did not show any clinically relevant changes. The z-scores in Figure 2 (online) allow cross-comparison of groups (as demonstrated by the 95% CI error bars) and show that, despite a significant increase in pain and discomfort (also described in Table 2), changes in SBP, HR and RR remained clinically irrelevant. This finding appears to be similar to previous reports on the effect of acute pain observed both in the ED and the prehospital environment.²⁰⁻²² These papers have without exception shown that—at least where acute injury is concerned—pain and vital signs showed no meaningful clinical correlation. As described in the introduction, the relationship between acute pain and the autonomic system has not been definitively described, and variability exists as to when a painful stimulus will result in a significant SNS response.⁸

One way to look at this is to consider the mechanism by which pain is induced (Table 3). Pain stimulated in the absence of tissue damage can be seen as physiological (protective or warning), whereas pain stimulated in the presence of tissue damage is pathological, as tissue injury has already occurred.²³ The specific course of the pain is also important (Table 3): phasic pain describes a short duration, high intensity pain, usually as trauma or tissue injury occurs. Acute pain following trauma or tissue injury not only has a phasic component but usually also a tonic component that continues at a lower intensity which can last for hours to days.²³ In spinal immobilization, discomfort and pain worsen with full immobilization, and are reduced when restraints are relaxed or removed (Figure 2, online). In this study there was no phasic component, a relatively low tonic component of pain (median pain VAS = 0), and discomfort (a proxy for tissue ischemia) after ten minutes reached only a median VAS of 15 (out of 100). This appears not to be sufficient to cause a clinically detectable SNS response, and it would seem that a more intense or prolonged

Mechanism of pain
<ul style="list-style-type: none"> • Physiological pain: painful stimulus in the absence of tissue damage; • Pathological pain: painful stimulus in the presence of tissue damage.
Course of pain
<ul style="list-style-type: none"> • Phasic pain: short duration, high intensity pain usually at the time tissue injury occurs (eg, phlebotomy); • Acute pain: includes the phasic component and then a tonic phase where pain resolves over hours to days (eg, sprained ankle); • Chronic pain: persists for longer than what is normally expected for healing and recovery (eg, complex regional pain syndrome).

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Table 3. Definitions Relating to the Course and Mechanism of Pain²³

stimulus (or both) would be required for the SNS effect to become clinically relevant.²³

It is thus important to consider other causes of abnormal vital signs, such as hemorrhage, head or spinal injury, associated medical problems or medications.² The relationship between hemorrhage and abnormal vital signs has been well described, but even here it should be noted that normal vital signs are not unusual in some cases, despite significant hemorrhage.^{2,3} Anxiety, too, may increase serum catecholamine and cortisol levels and decrease baroreflex sensitivity, resulting in abnormal vital signs.^{24,25}

Limitations

There are a few limitations to this study which are important to note. The study took place outside the true clinical setting. The study protocol allowed for a relaxed environment, employing a procedure all participants were familiar with. This was purposeful in order to reduce the possible confounding effect of anxiety. This study was not powered to allow subgroup analysis of gender differences that may have applied, and it is possible that the female predominance may have affected results. It is also possible that a longer period of spinal immobilization would have resulted in abnormalities. However, in the review of randomized controlled trials on the effects of spinal immobilization on subjects, Kwan et al⁹ referenced testing times of 10 minutes in three of the 10 studies reviewed. The current study was based on this figure, though in fact the immobilization lasted for 20 minutes (10 minutes fully immobilized and 10 minutes partially immobilized). In planning the study protocol, the authors felt that 10 minutes was a safe duration of exposure to a rigid spinal board. Given the low pain and discomfort scores

observed following 10 minutes of spinal immobilization, it is questionable whether further study is required to evaluate this. The subjects were uninjured and it is possible that the addition of discomfort from spinal immobilization to that already being suffered as a result of an injury might have more physiological effect than in an uninjured person.

Conclusion

Health care professionals working in the ED or prehospital environment should be aware that spinal immobilization does not contribute significantly to physiological derangements of SBP,

HR and RR. It would follow that when physiological derangements are present, these should be considered to be due to another cause. Likewise it is important to note that since pain and discomfort reported by patients with spinal immobilization do not correlate with vital signs, abnormal values should not be considered a prerequisite for the appropriate treatment of pain or discomfort.

Supplementary Material

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/S1049023X13000034>.

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Discussion of study

Methods

The power calculation was based on what is described in the paper as an *a priori consensus among authors* to determine difference in HR, SBP or RR from initial resting values that is clinically significant. These were a HR, SBP and RR of 10BPM, 7.5mmHg and 2.5bpm respectively. As the agreed minimum differences, these were also employed as outcome measures against which the eventual results could be checked. In order to come up with these values the sample size required to reject the null hypothesis was calculated for a mean HR difference of 10BPM (standard deviation (SD)=25, $\alpha=0.05$) when powered to 80%. The authors all agreed that in clinical practice a change in HR of 10BPM would be the minimum acceptable difference tolerated. The resulting sample size (52 subjects) was then used to calculate the mean SBP and RR difference, using the same α and power (SD=18 and 6 respectively), which turned out to be 7.5mmHg and 2.5bpm respectively. The authors all agreed that both results were also of a minimum acceptable difference. SDs were difficult to obtain given the novelty of this study and paucity in the literature; instead SDs were drawn from studies evaluating the effect of pain or transport on vital signs were used as a proxy.^{82,83,85,121}

One of the challenges in this study was to attempt to isolate the effect of pain and discomfort on vital signs. Obvious confounders such as PMCs, medications, pregnancy or existing back problems were easy to remove at recruitment. However, removing anxiety required a little more thought. For this reason data collection occurred separate from the ED in a quiet, unoccupied room with lights directly above subjects' switched off. Although not specifically measured during data collection, regular checks were made to subjects' well-being during data collection and the data collector (also the principal investigator) did not leave the room at any time. As a result no candidates reported feeling anxious at any point. With all these measures in place the principal investigator was satisfied that this study was able to isolate the effects of either pain or discomfort to a fairly good degree (although it is impossible to say whether it was truly eliminated).

Use of both pain and discomfort VAS initially proved controversial with co-authors. It was wondered what a discomfort score of 10 (the worst imaginable discomfort) meant and how this might differ from a pain score of 10 (worst imaginable pain). However previous studies have measured discomfort and it was felt that by having to pick one or the other, some

meaning might have been lost to the study; even though pain is usually uncomfortable, discomfort is not necessarily painful and immobilisation has been described in the literature to cause both pain and discomfort. Pain scores are standard practice in clinical medicine, with discomfort scores only really used in research. Out of twelve studies that were found to evaluate spinal immobilisation, six used pain and six used comfort/ discomfort as an outcome measure.^{86,87,89-91,122-129} Both pain and discomfort were used in these studies as a subjective measure of tissue ischaemia in pressure areas due to immobilisation and both were mostly measured using a VAS. As pain and discomfort scores were not used head-to-head in any of these studies it was unclear which would provide the most useful result. As such, both were included in the data collection. A standard explanation was given of what each means before data collection was commenced. Discomfort was described as a “feeling of being physically uncomfortable” and pain as an “acutely unpleasant physical discomfort”.^{130,131} It was expected that discomfort would be rated higher than pain, although this was not known beforehand.

The modified logroll described in this paper was performed by the data collector. A full logroll team was deemed excessive as none of the subjects were injured and as additional people may have resulted in a less calm atmosphere, thus affecting subjects’ level of anxiety. It was performed as follow: Head blocks were removed and the rigid collar was left in place. Whilst standing at the side of the trolley, the data collector asked the subject to flex the near-side hip and knee and hold on to the far-side trolley-rail with the near-side hand. The spinal board was then tipped about 30° towards the far-side of the trolley and gently slid out towards the data collector. The subject thus simply slid off the board and back onto the bed whilst supine and without having to sit or get up.

Friedman’s analysis of variance (ANOVA) was used to evaluate the repeated measures sample as not all of the variables were normally distributed. Parametric variables included HR and SBP, whilst RR, pain and discomfort VAS were all non-parametric variables. One option was to perform repeated-measures, one-way ANOVA for HR and SBP and Friedman’s ANOVA for RR, pain and discomfort VAS. Since non-parametric tests, including Friedman’s ANOVA, generally result in some loss of power compared to parametric tests this option would have afforded the best results for at least HR and SBP. However on analysis it was found that both HR and SBP violated the assumption of sphericity. Sphericity has to do with the equality of variances of the differences between the measures; in other words, if the differences between each pair of measures were calculated, then the approximate

variances of the differences should be equal. If not, then sphericity has been violated. As it stands, sphericity is not essential for repeated measures designs, but it does suggest that the resulting F-ratios are unreliable. Several statistical corrections (fixes) can be applied if sphericity has been violated although yet again all have some degree of trade-off: the Greenhouse-Geisser correction is regarded as too conservative (failing to reject false null hypotheses), the Huynh-Feldt correction overestimates sphericity and multivariate ANOVA (MANOVA) where power can be variable depending on sample size, the size of the violation and the relationship between measures. A final option was to simply conduct non-parametric testing on all variables. Indeed this would result in a trade off on power as mentioned earlier, but it would also provide consistency. Given the alternative options' repertoire of trade-offs, Friedman's ANOVA was settled on for use on all variables.¹³²

Friedman's ANOVA revealed significant differences for all variables, with pain and discomfort VAS having highly significant results. However, when the actual differences for HR, SBP and RR were compared with the outcome measures, the differences were negligible, despite being significant. Statistics is an interesting beast and quite often results may be confusing and not quite what it seems. As described before, SDs had to be extrapolated from pain and transport studies looking at differences in vital signs. As can be seen the SDs found in this study were actually quite smaller than those used to estimate the sample size. In fact if these SDs were used, the required sample size would have been 26 (exactly half of what was estimated using the extrapolated SDs). Still, a higher sample size is better than having an inadequate one as the latter would reduce power and thus increase the risk of a type 1 error. This finding highlighted the importance of setting outcome measures for studies exploring new ground. Outcome measures allowed a separate evaluation of the findings in table 1 of the paper revealing no clinically relevant differences (**Table 6**).

Bear in mind that Friedman's ANOVA only gives an overview impression of all group interactions, where the authors were mainly interested in the difference between the baseline (at rest) value versus that of each of the other four groups in turn. In addition, a significant result may mean anything from all group interactions being significant or that only one interaction out of all the group interactions is significant. It also doesn't reveal at which interaction the significant interaction is found. Therefore a post-hoc test (Wilcoxon signed-rank test) was done to see where the significant interaction lay. This is in keeping with the basic approach to comparing multiple experimental groups (whether parametric

or non-parametric): first perform an overall group test and if a significant result is found then post-hoc analysis is performed. This procedure is important since the former excludes family-wise error when performed, which would affect post-hoc tests if these were done from the outset. **Table 6** gives the results of post-hoc testing for the largest group difference for HR, SBP and RR (not in paper). In order to correct for the family wise error given five groups, significance is evaluated at a fifth of the standard 0.05 alpha level, thus $p < 0.01$ would signify significance (also called the Bonferroni correction). This clearly shows that although the group differences were significant, when compared with outcome measures they were not clinically relevant.

Table 6 Outcome measures, largest mean difference and standard deviation

Variable	Outcome measure	Largest mean difference	p
Heart rate (BPM)	10	-4*	0.001
Systolic blood pressure (mmHg)	7.5	-2*	0.008
Respiratory rate (bpm)	2.5	-1†	0.03

BPM, beats per minute; bpm, breaths per minute; *, at rest vs. partially immobilised; †, at rest vs. semi seated; p-values from Wilcoxon signed-rank test with Bonferroni correction, $p < 0.01$ describes significance

Finally this study received ethics clearance from two ethics boards. As part of the PhD protocol it received clearance from the University of Cape Town's human research ethics committee (HREC). Since it was performed in the United Kingdom in a NHS institution, it required clearance from the local authorities. An application was first made to the UCT HREC and following approval, a second application was made to the NHS South West 1 REC. As part of the ethics application to both RECs a subject consent form and information sheet was produced. These are included as **Appendix A and B** at the end of the thesis.

Results

The problem with variables that have different units of measure (i.e. BPM, mmHg and bpm) is that it is difficult to compare the effect between variables, unless the variables are of the same unit of measure. By transforming variables to z-scores datasets from different variables can be expressed in SD units (**Figure 1**). The calculation for z-scores is as follow: the pooled mean and SD for each variable (HR, SBP, RR, pain or discomfort VAS) is

calculated. The pooled mean is then subtracted from each sub-variable's mean and the result is divided by the pooled SD.¹³² For example, the pooled mean and SD for SBP is 113.5mmHg and 12.2 respectively. The mean z-score for SBP at rest would thus be $(114\text{mmHg} - 113.5\text{mmHg})/12.2=0.04$. The resulting data can now be inter-compared irrespective of the original units of measure. For instance, during full immobilisation discomfort VAS increased significantly more than HR, SBP or RR did (**Figure 1** and **Table 7**, both are published as online data supplements).

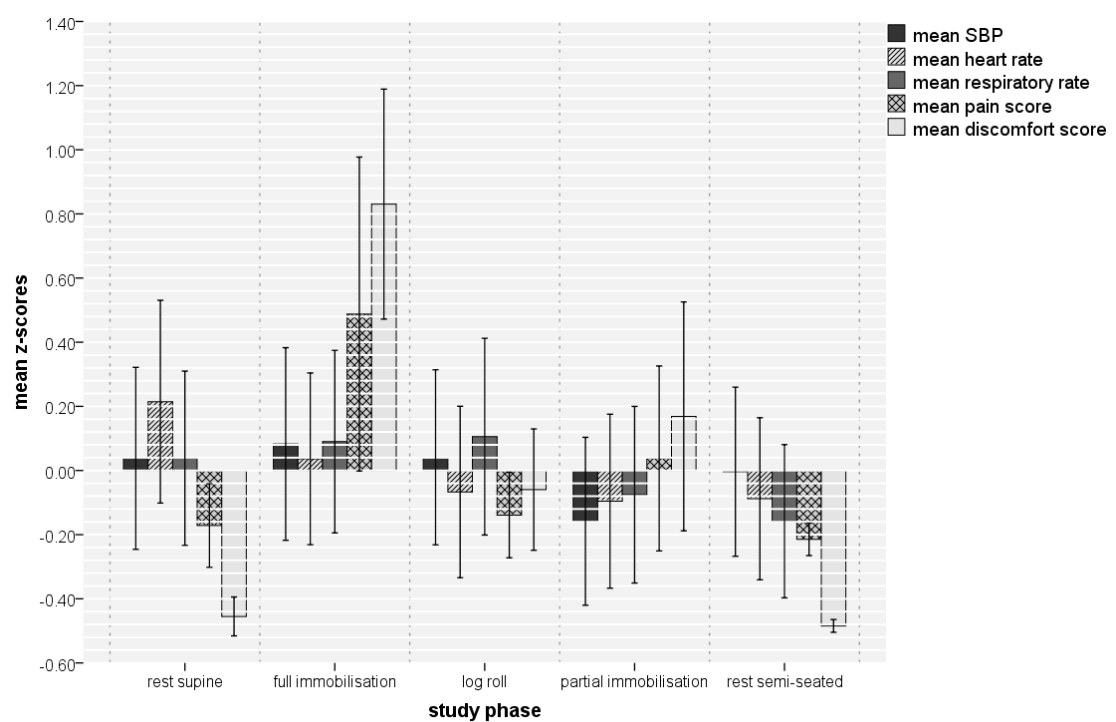


Figure 1 Comparing data sets using z-scores (95% confidence interval lines displayed for mean HR, SBP, RR, pain and discomfort VAS for each of the study phases

Table 7 Comparing different data sets using mean z-scores (95% CIs)

Vital sign	Rest supine	Fully immobilised	Log roll	Partial immobilised	Rest semi seated
Systolic blood pressure	0.04 (-0.25 to 0.32)	0.08 (-0.22 to 0.38)	0.04 (-0.23 to 0.31)	-0.16 (-0.42 to 0.10)	0 (-0.27 to 0.26)
Heart rate	0.21 (-0.10 to 0.53)	0.04 (-0.23 to 0.30)	-0.07 (-0.33 to 0.20)	-0.10 (-0.37 to 0.18)	-0.09 (-0.34 to 0.16)
Respiratory Rate	0.38 (-0.23 to 0.31)	0.09 (0.19 to 0.37)	0.11 (-0.20 to 0.41)	-0.08 (-0.35 to 0.20)	-0.16 (-0.40 to 0.08)
Pain VAS	-0.18 (-0.30 to -0.04)	0.49 (0 to 0.98)	-0.14 (-0.27 to -0.01)	0.04 (-0.25 to 0.33)	-0.21 (-0.27 to -0.16)
Discomfort VAS	-0.46 (-0.52 to -0.39)	0.83 (0.47 to 1.19)	-0.06 (-0.25 to 0.13)	0.17 (-0.19 to 0.53)	-0.49 (-0.50 to -0.46)

It is important to understand that z-scores do not tell us anything about the pain or discomfort VAS's effect size and thus the question remained whether the painful or uncomfortable stimulation employed through immobilisation was in fact relevant at all. The implication would be that if the effect of immobilisation on the pain or discomfort VAS was small (similar to HR, SBP and RR) then either immobilisation is not very painful or uncomfortable, or contact time was not sufficiently long for pain or discomfort to develop. As described in the paper's methods section, Pearson's correlation coefficient (r) was used as a measure of effect size. Probably more widely known as a measure of the strength of a relationship between variables, Pearson's r is also widely used in the social sciences to denote effect size. To calculate r one simply has to divide Z (from Wilcoxon signed-rank test output) by the square of all observations. Since both Z and the number of observations are known the calculation wasn't too difficult. A large effect would be an r greater than 0.5, medium an r greater than 0.3 but less than 0.5 and a small effect an r less than 0.3.¹³²

Table 8 shows the effect sizes for HR, SBP and RR in addition to pain and discomfort VAS (also in table 2 from paper) with respect to the difference between subjects at rest and fully immobilised. This clearly shows a small effect for pain, but a large effect for discomfort. The effect for vital signs was also small. The likely deduction from this would be that ten minutes of full immobilisation did not affect the vital signs, nor was it very painful. It was however uncomfortable.

Table 8 Effect sizes for variables at rest compared with variables fully immobilised

Variable	Z	r	Meaning
Heart rate	-2.15	-0.21	Small
Systolic blood pressure	-0.93	-0.09	Small
Respiratory rate	-0.65	-0.06	Small
Pain VAS	-3.01*	-0.29	Small
Discomfort VAS	-5.97*	-0.58	Large

r , Pearson's correlation coefficient; VAS, visual analogue scale; *, denotes a significant difference ($p < 0.01$)

Table 9 Additional descriptive statistics (reference value in bold)

Variable	Median	Interquartile range (IQR)	
		Lower	Upper
RR at rest	14	12	16
RR fully immobilised	14	12	16
RR after log roll	14	10	16
RR partial immobilised	14	10	16
RR semi seated	14	12	16
Pain VAS at rest	0	0	0
Pain VAS fully immobilised	0	0	0.7
Pain VAS after log roll	0	0	0
Pain VAS partial immobilised	0	0	0
Pain VAS semi seated	0	0	0
Discomfort VAS at rest	0	0	0
Discomfort VAS fully immobilised	15.1	3.4	24
Discomfort VAS after log roll	2.1	0	9.6
Discomfort VAS partial immobilised	2.1	0	9.6
Discomfort VAS semi seated	0	0	0

RR, respiratory rate; VAS, visual analogue scale

Finally, for non-parametric variables RR, pain and discomfort VAS the median described the central tendency whilst for parametric variables HR and SBP the mean fulfilled that role. The measure of precision suitable for parametric variables was given as confidence intervals (table 1 in the paper), but due to space constraints a suitable measure of precision

for non-parametric variables (interquartile rang, IQR) were omitted. The IQR is described in **Table 9** for RR, pain and discomfort VAS.

Limitations

As mentioned in the paper, the study was not powered for subgroup analysis and therefore gender differences could not be explored. There was however a disparity between male and female participants with nearly four times more females enrolled. Experimental studies have shown that given an acute, painful stimulus, HR is significantly less likely to increase in females than males.¹³³⁻¹³⁵ If one considers that in this study, spinal immobilisation had a stronger effect on HR than on SBP or RR (**Table 8**), it could perhaps be argued that if more men were enrolled a larger effect may have been seen, which may have pushed HR into clinical significance. In order to debate this point, one would have to consider the differences in methodology between this study and the referenced experimental studies. These evaluated a response to an intense, painful stimulus (phasic pain) which is different from the lack of phasic pain associated with spinal immobilisation from this study. As a result, a physiological response was less likely from the outset. In addition, clinical studies into the clinical effect of pain on HR in the ED have not reproduced experimental findings despite pain scores as high as a median of seven.^{82,83,85} In this study, neither the pain, nor discomfort VAS were nearly that high (table 1 from the paper; note that a conversion applies from the 100mm VAS used in this study vs. mainly a 10-point VAS used in the referenced clinical studies). Also as the pain from the clinical studies was unlikely to still be considered phasic, but rather in the tonic phase, parallels could perhaps be drawn as to why no clinical effect were seen in those either. This was however beyond the scope of the paper.

The duration of immobilisation lasted 10 minutes with full immobilisation and 10 minutes with partial immobilisation. It can be argued that if full immobilisation on the rigid spinal board lasted longer that pain would have increased and that this may in time have led to a clinically significant change in vital signs. Although this is possible, it is already known that sustained pain in the ED does not lead to any significant changes in vital signs.^{82,83,85} The pain or discomfort from being immobilised on a rigid spinal board is best described as physiological and not pathological (table 4 in the paper).¹²⁰ The difference relates to the presence of tissue injury; physiological pain relates to anticipation of injury (i.e. painful heat stimulation) and pathological pain is present when pain had already occurred (i.e. burn). Pathological pain is often accompanied by sensitisation leading to continued pain despite

removal of the stimulus. In contrast, physiological pain is often associated with down modulation of the response to pain. In addition to the pain from spinal immobilisation being of a physiological nature, it also has no phasic component (as described in **Table 5**). In the experimental studies pain was related to a significant rise in HR, but that was because of a phasic component to the experiment.¹³³⁻¹³⁵ As this is absent, it is hardly surprising that no clinically significant change in vital signs was observed. Whether or not vital signs would be affected if immobilisation was prolonged so long that it resulted in enough tissue ischaemia to produce pressure ulcers is not known. The 10 minutes of spinal immobilisation was long enough to establish whether pain from immobilisation had an initial phasic component. Longer immobilisation up to the recommended limit of 45 minutes by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) is unlikely to have had any additional effect given the physiological nature of the pain.¹³⁶ Immobilisation beyond that timeframe would have been unsafe to perform. It is beyond the scope of this study to speculate on vital sign changes that might be associated with tissue injury resulting from spinal immobilisation.

Chapter conclusion

Neither spinal immobilisation, nor any of the manoeuvres commonly used in injured patients appear to result in any clinically relevant changes in vital signs and therefore when present, abnormal vital signs should be treated as from a different origin. In addition, abnormal vital signs should not be sought as a prerequisite to treating pain and discomfort as a result of immobilisation. Building on this finding, **Chapter 3** looks a little closer at the WCE due to trauma by comparing the vital signs of an uninjured with a moderately injured cohort in a case-control design; some of the findings which have already been alluded to in this chapter. **Chapter 4** of this thesis regards the effect of ambulance transport on vital signs. Given the findings of this study, the effect of spinal immobilisation should not need to be considered as contributory to any effect resulting from ambulance transport.

Chapter 3

The difference between vital signs associated with minor to moderate injury and healthy subjects

Reference

Bruijns SR, Guly HR, Bouamra O, Lecky F, Wallis LA. Heart rate and systolic blood pressure in patients with minor to moderate, non-haemorrhagic injury versus normal controls. *Emerg Med J.* 2013;30(11):901-905

Declaration of author

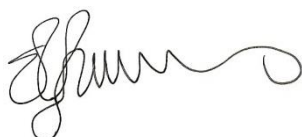
In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

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- **Nature of contribution:** SRB and HRG came up with the original idea; SRB did the majority of planning, wrote the first and subsequent drafts of the proposal, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript and this chapter and is the corresponding author and guarantor of the publication; HRG and LAW contributed to the proposal, manuscript and chapter; OB contributed to the statistical planning and analysis and manuscript; FL contributed to the planning and manuscript
- **Extent of contribution:** SRB: 75%; HRG: 10%; LAW: 5%; OB: 5%; FL: 5%

The following co-authors contributed to the work

1. Prof. Lee A Wallis
2. Dr. Henry R Guly
3. Dr. Omar Bouamra
4. Prof. Fiona Lecky



Signed: Stevan R Bruijns

Declaration by co-authors

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other author of the publication according these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from date indicated below


Location of stored data: Raw data are stored with the respective databases, the Health Survey for England and the Trauma Audit and Research Network. Manipulated data are stored within a password protected database at Plymouth Hospitals NHS Trust, Plymouth, United Kingdom.



Prof Lee A. Wallis

15 July 2013

Date



Dr Henry R. Guly

15 July 2013

Date

Main findings

- Heart rate is approximately 10BPM higher in a minimally injured, non-haemorrhagic cohort compared to an uninjured one, irrespective of age
- There are no clinically relevant differences between SBP in a minimally injured, non-haemorrhagic cohort compared to an uninjured one, irrespective of age
- There are no clinically relevant difference between either HR or SBP in a spinally immobilised cohort compared to a non-immobilised one, irrespective of age

Argument for conducting study

Anxiety is one of the elements involved in trauma care that may affect vital signs, along with spinal immobilisation and ambulance transport as discussed in **Chapter 1**. It has already been shown in **Chapter 2** that spinal immobilisation and the manoeuvres employed during spinal immobilisation do not affect HR, SBP or RR. **Chapter 4** will also show the minimal effect of emergency transport. Dark, et al. showed that children will have an increased SBP following blunt trauma relative to the SBP of children at rest.¹³⁷ WCE has however not been studied in an adult ED setting despite the implications it might have for patients. It seems possible that when sufficient injury is present, an anxiety effect can be attenuated and therefore changes to HR are only expected if injury is minor. It follows that anxiety may result in changes to HR and SBP that may confuse clinicians suspecting this to be due to injury or haemorrhage. It is therefore important to understand how anxiety affects the HR and SBP of minimally injured, non-haemorrhagic patients in order to factor this into trauma care. In addition, this study provided the opportunity to confirm the experimental findings of **Chapter 2** using a much larger sample size. As a result, it was expected that the null hypothesis would be rejected for both HR and SBP in the anxiety part of the thesis but accepted in the immobilisation part.

Aim

To compare the relationship between the HR and SBP respectively between immobilised and non-immobilised patients, and the relationship between the HR and SBP respectively in non-haemorrhagic, minimally injured patients and those of a non-injured control group.

Objectives

1. Comparing the HR and SBP in non-haemorrhagic, minimally injured patients with the HR and SBP of a non-injured control group for different age groups, using large national databases
2. Within the injured group, to compare the HR and SBP of subjects requiring spinal immobilisation with the HR and SBP of subjects that did not require spinal immobilisation for different age groups

A copy of the published paper follows on the next five pages

University of Cape Town

Heart rate and systolic blood pressure in patients with minor to moderate, non-haemorrhagic injury versus normal controls

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Additional data are published online only. To view these files please visit the journal online (<http://dx.doi.org/10.1136/emmermed-2012-201760>).

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ABSTRACT

Background Raised blood pressure (and heart rate (HR)) due to anxiety in a clinical situation is well described and is called the white coat effect (WCE). It is not known whether the pain and anxiety that results from trauma causes a measurable WCE.

Methods A sample of patients with a non-haemorrhagic injury from the Trauma Audit and Research Network (TARN) was compared with a healthy, non-injury sample from the Health Survey for England (HSE) databases. Two-way analysis of variance with rank transformation of data was used to compare systolic blood pressure (SBP) and HR between the groups at different ages. In the injured group, the SBP and HR were also compared between spinally immobilised and non-immobilised patients.

Results There was a statistically significant difference between the groups for both HR and SBP ($p < 0.001$). Median HR remained approximately 10 bpm higher in the TARN set when compared to the HSE set, irrespective of age. The difference for SBP was not considered clinically relevant (the highest was 5 mm Hg). There was no significant difference between immobilised and non-immobilised patients, for either HR or SBP ($p = 0.07$ and 0.3, respectively).

Discussion Median HR remained approximately 10 bpm higher in the TARN (injury) set compared to the HSE (non-injury, control) set, irrespective of age. Understanding that HR reacts in this way for mild to moderately injured patients is important as it will affect clinical interpretation during the initial assessment.

mitigation of the vagal component of the receptor (the exact mechanism still eludes scientists).⁶ However, only severe pain induces any clinically distinguishable effect and even then the result can be variable.⁶⁻⁸ Haemorrhage, injury and pain (each exerting its own effect) all contribute to the changes in vital signs which result from trauma.²

Anxiety can induce an increased BP and HR without the presence of injury, haemorrhage or pain.⁹⁻¹⁰ The white coat effect (WCE), associated with anxiety,¹¹⁻¹² is well described and refers to a raised BP (and HR) observed when patients present in a clinical situation.¹¹⁻¹² A comprehensive search of the literature (including the British Nursing Index, EMBASE, CINAHL, MEDLINE and Google Scholar) revealed no studies on WCE in a trauma setting. It is thus not known whether a WCE is observed in the trauma setting, and if it is, whether it can be related to simple trauma adjuncts such as spinal immobilisation. If the WCE in a trauma setting was known, this could be factored in during the evaluation, allowing distinction from what is less relevant and what is likely to be of clinical concern.

The primary aim of this study was to compare the relationship between HR and systolic BP (SBP) in non-haemorrhagic, minimally injured patients with that of a non-injured control group. A secondary objective was to compare within the injured group those that required spinal immobilisation and those that did not. The null hypothesis for all objectives was that no difference existed.

INTRODUCTION

Evaluation of an injury includes assessment of a patient's vital signs in order to make an early judgement of the patient's condition.¹ However, this is not straightforward, as vital signs in trauma are affected by raised intracranial pressure, spinal cord injury, tissue damage, haemorrhage, pain and anxiety.² Despite widespread use of Advanced Trauma Life Support (ATLS) principles, their guidance relating to haemorrhage and vital signs lacks evidence.³⁻⁴ In particular, ATLS does not appear to acknowledge either the vagal response to pure haemorrhage which results in a bradycardia, or the effect of tissue injury.⁴ Tissue injury alters the cardiovascular response to haemorrhage, by attenuating the vagal response (resulting in slightly higher blood pressure (BP) and heart rate (HR)).²⁻⁵ This is largely due to a prevailing sympathetic outflow as the result of decreased baroreflex receptor sensitivity induced through the tissue injury. Pain appears to affect baroreceptor sensitivity, but through

METHODS

Permission was obtained from the Trauma Audit and Research Network (TARN) and the Health Survey for England (HSE) to use data from their respective databases to perform a retrospective case-control study. The TARN database is the largest trauma database in Europe, collecting data related to trauma patients from a group of collaborative hospitals in England and Wales since 1989. The HSE is an annual national health survey representing people of different age, sex, geographic area and socio-demographic backgrounds in England.¹³ This study was approved by the Research Ethics Committee of the University of Cape Town, South Africa (reference 014/2010). The HSE data would be representative of a physiologically unstressed population such as might attend a UK emergency department (ED) following trauma. The TARN data was used as the test group and the HSE data as the control.

Original article

Subjects from either database were included if they were older than 16 and had SBP and HR recorded. Respiratory rate was not included as this is not part of the HSE dataset. Both datasets drew their respective samples from the period 1996 to 2006. The HSE sample included subjects who had eaten, drank alcohol, smoked or exercised vigorously within the 30 min preceding measurement in addition to subjects who did none of these. Specific inclusion criteria for the TARN sample were patients with upper extremity, or below-knee, lower extremity injury. In order to ensure an injury sample that did not include haemorrhage as a cause for deranged vital signs, subjects in the TARN database with the following were excluded:

- Amputation, crush, degloving, penetrating, laceration, skin avulsion or vessel injuries present
- Open fractures, scapular injuries, femur or pelvic injuries
- Additional injuries other than minor injury
- Glasgow Come Score less than 15, intubated or cardiopulmonary resuscitation required
- More than 1 litre fluid used (prehospital and/or ED)
- Only partial spinal immobilisation used

Median, IQR, mean, SD and 95% CIs were used to describe different datasets. Although not typically reported for non-parametric data, mean and SD were included to compare to the reference range for HR given in a study mentioned in the discussion section.¹⁴

An age variable consisted of seven age categories grouped as follows: 16–25, 26–35, etc, with all those aged over 75 grouped together. A further two variables included an injury variable (HSE or TARN) and an immobilisation variable (full immobilisation or no immobilisation). A two-way analysis of variance (ANOVA) was done to compare the mean SBP and HR between the injury variable, and the immobilisation variable, respectively, using the age variable as the additional factor for each analysis. Rank transformation of SBP and HR was required since the real data violated the assumption of normality. Use of rank transformed data in parametric tests (including a two-way model) generally compares well with non-parametric test results in terms of robustness and power. This approach provides a novel solution where non-parametric alternatives are not readily available, such as with two-way ANOVA.¹⁵

A *p* value of less than 0.05 was considered statistically significant.¹⁶ Outcomes measured were the difference for HR and SBP between the TARN and HSE datasets, and the fully immobilised and non-immobilised datasets, respectively. The literature suggests that a clinically relevant WCE effect is likely to cause SBP to increase by 25–30 mm Hg and the HR to increase by 10–15 bpm.^{11–12} Values of 25 mm Hg for SBP and 10 bpm for HR were used as outcome measures for this study.

RESULTS

Table 1 presents the different datasets used. The disparity in data between the TARN sample and the full/non-immobilised samples relates to 1930 TARN cases where immobilisation data were not available. These data points were included for analysis in the larger TARN sample, but not the immobilisation variable.

Two-way ANOVA of rank transformed data showed that there was a significant main effect of injury on both the HR and SBP (*p*<0.001). The main effect of age was also significant for both HR and SBP (*p*<0.001). There was a significant interaction effect between the injury and age variables, for both HR and SBP (*p*<0.001). This result indicates that the vitals in the no injury (HSE) and injury (TARN) groups were affected differently by age. These differences are shown in figure 1A,B. In real

Table 1 Descriptive statistics for the injury and immobilisation variables

	Injury variable		Immobilisation variable	
	HSE	TARN	Not immobilised	Fully immobilised
N (cases enrolled)	98399	40906	37567	1409
Mean age	47	52	53	45
% Male	46	48	46	64
Heart rate (bpm)				
n (%)	98294 (99.9)	40745 (99.6)	37421 (99.6)	1400 (99.5)
Missing (%)	105 (0.1)	161 (0.4)	146 (0.4)	9 (0.5)
Mean (SD)	70.8 (11.1)	80.9 (14.6)	80.9 (14.6)	81.5 (15.1)
95% CI	70.7 to 70.9	80.8 to 81.1	80.7 to 81	80.7 to 82.3
Median	70	80	80	80
IQR	63–78	71–90	71–90	70–90
Systolic BP (mm Hg)				
n (%)	98173 (99.8)	40829 (99.8)	37492 (99.8)	1407 (99.9)
Missing (%)	226 (0.2)	77 (0.2)	75 (0.2)	2 (0.1)
Mean (SD)	133.2 (18.9)	138.6 (24.9)	138.6 (25)	138.6 (23.1)
95% CI	133 to 133.3	138.4 to 138.9	138.4 to 138.9	137.4 to 139.8
Median	131	136	136	137
IQR	120–143	120–153	120–153	122–152

HSE, Health Survey for England; TARN, Trauma Audit and Research Network.

values, median HR remained approximately 10 bpm higher in the TARN set when compared to the HSE set, irrespective of age, and this value satisfied the outcome measures (figure 2). SBP in the TARN set was higher than the SBP in the HSE set at younger ages, but this difference reduced dramatically in the older age groups. The difference (although significant in some groups) did not satisfy the outcome measures at any point. Tables S2 and S3 (data supplement) show the descriptive statistics for HR and SBP, respectively, for the injury–age variables' interaction.

Two-way ANOVA of rank transformed data showed that the effect of immobilisation on the HR was not significant (*p*=0.36). The effect of immobilisation on SBP was significant (*p*<0.001). There was no significant interaction effect between immobilisation and age, for either the HR or SBP (*p*=0.07 and 0.3, respectively), indicating that the vital signs in the no immobilisation and full immobilisation groups were not affected differently by age. These differences are shown in figure 1C,D. Although the SBP in the fully immobilised set was higher than the SBP in the non-immobilised set throughout the age groups, this difference was not clinically significant. This is shown in table S4 (data supplement). As the difference in HR was not significant for either immobilisation or its interaction with age, descriptive data are not reported.

DISCUSSION

The most pertinent finding was that median HR remained approximately 10 bpm higher in the TARN (injury) set compared to the HSE (non-injury, control) set, irrespective of age. SBP was slightly higher in younger age groups (<56 years), but although statistically significant, even the highest mean difference (5 mm Hg) was considered clinically irrelevant when compared with a BP rise expected due to a WCE (25–30 mm Hg). No statistical differences were found between the immobilised and non-immobilised groups for HR, and the difference found with SBP was not considered clinically relevant.

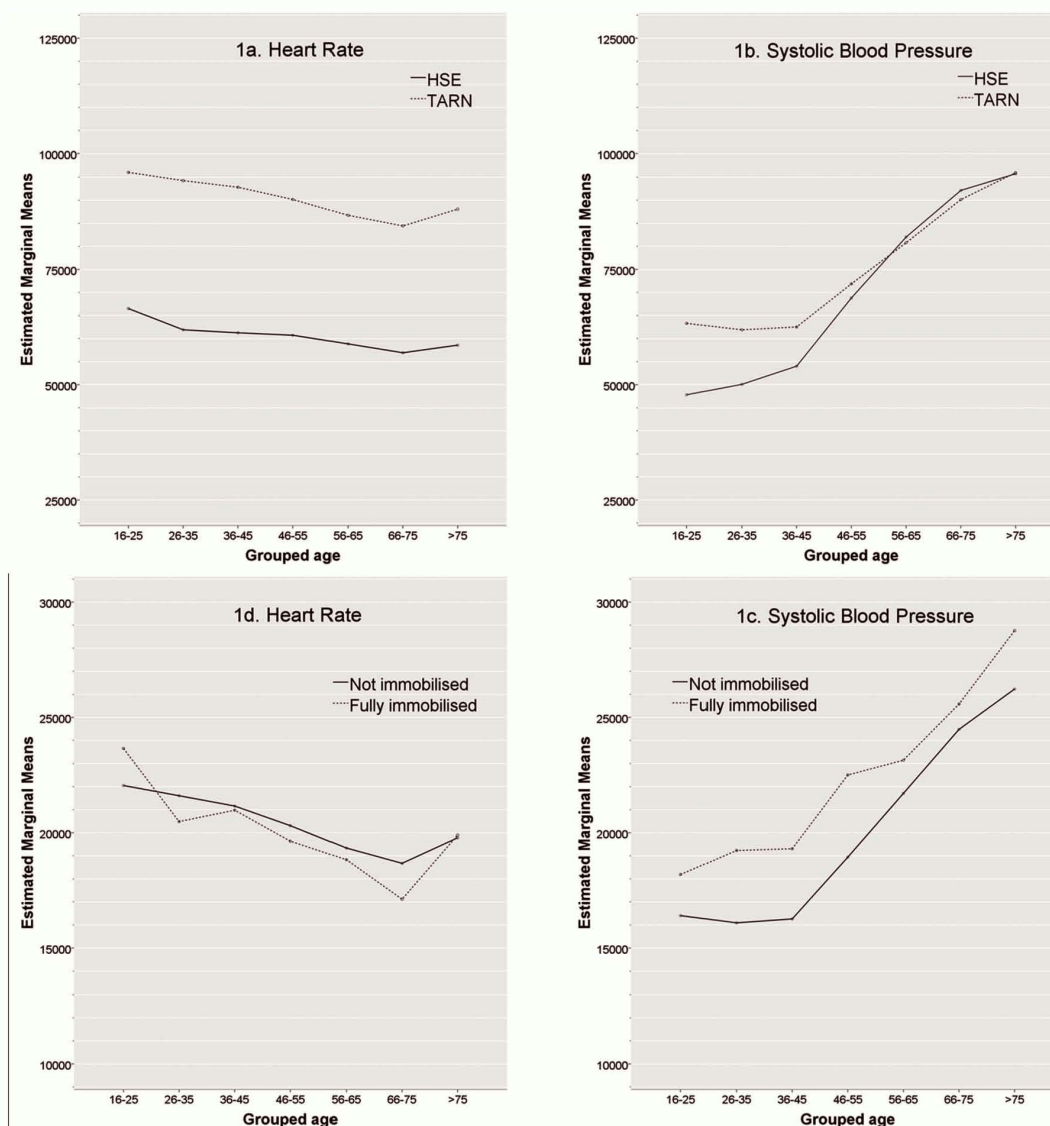


Figure 1 (A–D) Clockwise from top left, interaction between age (x-axis) and injury variable for heart rate (HR) and systolic blood pressure (SBP), interaction between age and immobilisation variable for SBP and HR (rank transformed, marginal means of either HR or SBP on y-axis).

These data suggest that the upper limit for the 'normal' HR in injured patients may need to be reconsidered. In order to determine this, one has to consider the calculations that derived the reference range of the current accepted standard (60–100 bpm). This reference originates from a publication of the New York Heart Association in 1928.¹⁷ Interestingly, its basis was to a large extent due to the fact that 60 and 100 bpm, respectively, represented five and three small blocks on an ECG recorded at 25 mm/s.^{15 18} A statistical solution followed using the mean \pm 2 SD (included in table 1).¹⁴ This approach drew criticism since HR is known not to be normally distributed.¹⁸ The mean is therefore not robust enough to describe central tendency in this skewed sample. An alternative approach suggested was to use IQR.¹⁸ This approach was based on the observations made in several studies showing increased cardiovascular risk when resting HRs were found to be in the upper quintile of a sample's distribution.^{19 20 21}

Interestingly in our sample, the 25th and 75th HR centiles increased, similar to the median, by approximately 10 bpm from the HSE to the TARN dataset. Mean HRs maintained the 10 bpm difference (with very minimal variation) throughout all age groups evaluated. It is not known whether this increase in HR increases cardiovascular risk as well, or how long this relative tachycardia will be sustained following injury. As no haemorrhage occurred in our sample population and it is known that less than severe pain has a very limited effect on vital signs,^{7 8} this relative tachycardia is more likely to be the result of anxiety, injury or a combination of anxiety and injury.⁶ Whether anxiety was the result of a WCE or directly related to the trauma event is debatable. Longitudinal studies have previously looked at HR in the ED as a predictor of post-traumatic stress disorder (PTSD) and found that the resting HR (at 1 month post-ED attendance) was lower than that recorded in the ED in non-PTSD groups (PTSD groups had even higher ED

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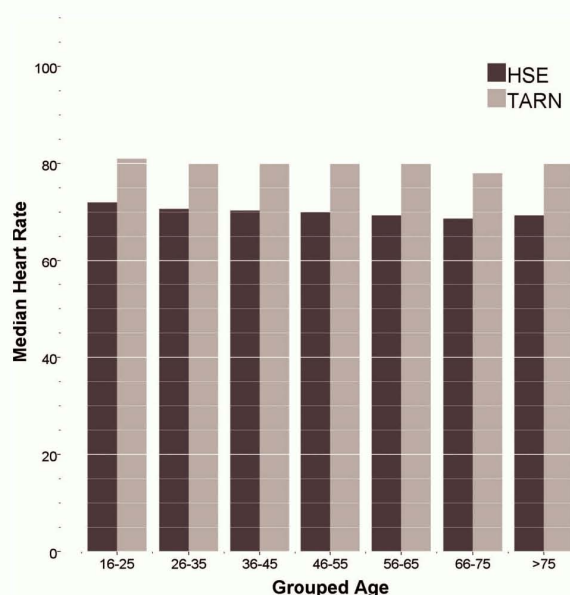


Figure 2 Median heart rate between Health Survey for England and Trauma Audit and Research Network groups within each age group.

HRs, with resting HRs similar to the non-PTSD group).^{22 23} The difference ranged between 6 and 11 bpm depending on the study. The difference in the PTSD groups was higher (0.5 and 13 bpm, respectively). The difference seen in the non-PTSD subjects were put down to subjects 'expressing a stress-response'.²⁴ It seems plausible that the 10 bpm difference seen in our study was due to a similar stress-response and that this stress-response was not affected by spinal immobilisation. Younger patients in this study tended to have higher SBPs, although this was not clinically relevant. Previously it has been noted that in blunt injured children, SBP was higher than was seen in similarly aged children at rest. This difference appeared to be unrelated to injury severity.²⁵ HR, although higher than seen in the *at-rest* group, was not significantly different from a resting baseline HR.²⁵ In our sample, SBP was higher in the injured population in lower age groups, although this difference was not considered clinically relevant. It is likely that the SBP difference increases with decreasing age.

Limitations

The authors are aware of the inherent information and selection biases associated with case-control studies from unrelated databases and results should be interpreted with these in mind. The large sample sizes yielded statistically significant results despite low clinical relevance. Arguably, deciding what is clinically relevant can be tricky as it is often open to interpretation. Ensuring that clear outcome measures were included in the design was a way to define clinical relevance and turned out to be a useful guide to interpret results.

CONCLUSION

Changes seen in the vital signs of patients with injuries have complex mechanisms and include haemorrhage, injury, fear and pain. This study has shown that as far as mild to moderate injury is concerned, HR tends to be higher than that expected in

an uninjured person. Differences seen in this study due to spinal immobilisation are also not likely to be clinically relevant. Understanding that HR reacts in this way for mild to moderately injured patients is important as it will affect the way we interpret the HR during the initial assessment. Clinicians should be aware of this occurrence so as to not confuse mild to moderately injured patients with a more severe cohort. More work is required to evaluate this phenomenon further.

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Data sharing statement All results from analysed data have been presented in this paper. Raw data are available from the TARN and the HSE to bona fide researchers on request.

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Discussion of study

Methods

A significant amount of planning went into the design of this case-control, observational study. Since a WCE had not been investigated in an ED cohort before, use of an observational design was considered useful to test the hypothesis in the first instance. A cohort design was initially considered although this turned out to be less practical given the variability with which patients' HRs would return to a baseline level following injury. The association between the time for the HR to return to normal following an injury and the incidence of PTSD has been investigated. From these studies it appears that this can vary between a week to a month.^{95,138,139} It would also require follow-up which would suggest that a prospective arm would be required. Furthermore, such a design would be limited to a smaller, locally managed sample size. Given the availability of the sizeable databases used in the study, a case-control design was chosen.

Since the TARN database was chosen as the source for the injured group, a database drawing from the same population was required for the control (uninjured) group. The Health Survey for England (HSE) seemed most appropriate.¹⁴⁰ HSE collects health and anthropomorphic data as part of an annual health survey in England, whilst TARN draws its injury data from participating EDs in England and Wales. HSE collects data at the subject's home whereas TARN collects data at the point of care, including the whole trauma patient journey from injury to discharge. Arguably there may be groups of patients which are more prone to injury (such as the elderly, children and those from a lower socio-economic status)^{4,141} who might be underrepresented in the HSE control. Given that children were excluded and that the elderly are generally well-represented in the English population, this was considered unlikely to be a cause for bias. In addition, subjects included in the HSE database were not excluded due to eating, drinking alcohol, smoking or exercising within the 30 minutes prior to data collection, thus making up a control group profile likely to be very similar to the TARN group, but without acute injury. RR was not included since it is not part of the HSE data sample and also not known to be altered by the WCE.

The Abbreviated Injury Scale (AIS) was used to select the TARN sample. AIS is a well-accepted anatomical coding resource used to describe and classify injury by location, type of tissue involved (vessel, nerve, bone, etc.) and the nature of the injury (avulsion, burn, crush, etc.).¹⁴² For each injury a corresponding AIS code denotes the level of severity which

is described in **Table 10**. AIS forms the basis for the calculation of the ISS which uses the three most severe injuries according to AIS code to generate the score. Due to the comprehensive nature of the AIS, it was also used to select subjects for this study as described in the paper.

Table 10 AIS codes

AIS code	Description	Example
1	Minor	Ankle sprain
2	Moderate	Ankle fracture
3	Serious	Neck of femur fracture
4	Severe	Pelvis fracture with less than 20% blood loss
5	Critical	Pelvis fracture with more than 20% blood loss
6	Maximum (incompatible with life)	Hepatic avulsion
9	Unknown	

AIS, abbreviated injury scale

Non-parametric analysis was required since data were found to violate the assumption of a normal distribution. However, the preferred model in which the injury variables (HSE vs. TARN) and immobilisation variables (full vs. none) were compared (as the first factor) with the age variable as described in the paper (the second factor) required a two-way, independent ANOVA for which a non-parametric alternative does not exist. Despite ANOVA being considered robust, even in instances when the assumption of a normal distribution is violated, it is not ideal due to a loss of control of type I error and therefore loss of power. One option was to renege on the factorial design and simply run a Mann-Whitney test to compare the two injury variables (HSE vs. TARN) and two immobilisation variables (full vs. none), and omit seeking for an age interaction. This would have been unfortunate as it is already known that age does affect both HR and SBP and understanding the interaction would have been very useful.^{2,41}

An alternative option to overcome this was to use rank transformed data from the dataset and to use this to run the two-way ANOVA as described by Conover et al.¹⁴³ Rank transformation lies at the basis of most non-parametric tests. Rank transformation is performed by finding the lowest value in the dataset and assigning it a rank of one. The second lowest value is then ranked two and so on and so forth. The transformed sample thus ends up with high rankings corresponding to high values from the dataset and low rankings with low values.¹³² The resulting transformed sample is then used to perform the parametric test instead of the original values. This method does result in a reduction of test power, but so would any parametric test performed on data that violated the assumption of a normal distribution. In addition it should be noted that a large sample would increase power (noting that only 52 subjects were required in **Chapter 2** to adequately power that sample and that turned out to be an overestimation). Because this study made use of such a large sample, a sample size calculation was not performed (as per convention in samples of this size) and by implication power was accepted to be more than adequate.

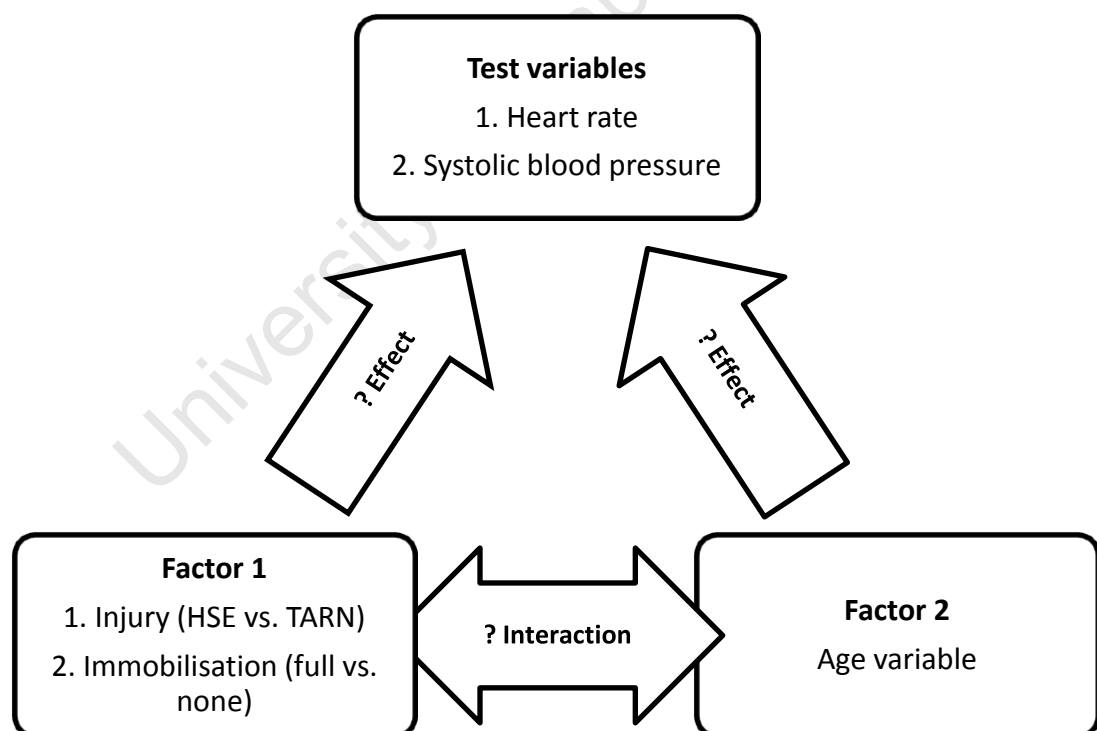


Figure 2 Diagrammatic description of two-way ANOVA; only one test variable (heart rate or systolic blood pressure) and one factor one variable (injury or immobilisation) were used per analysis

One more shortfall of performing two-way ANOVA on rank transformed data is that the output results would no longer be recognisable as HR or SBP units. However, this did not distract from the objectives of this study which were mainly looking for the effect of the three variables on HR and SBP, and the interaction between the variables. Median differences could easily be calculated separately and compared to the outcome measures which were set up before the start of the study. These are described in the paper and are based on the lowest ranges used in the literature that defines a WCE; 10BPM for HR and 25mmHg for SBP.^{18,19} With these provisos, a two-way ANOVA of rank transformed data was performed (**Figure 2**).

Results

The most interesting finding was that HR remained approximately 10BPM higher in a moderately injured cohort compared with the healthy cohort and that this was consistent, irrespective of age (**Table 11**). As SBP remained mostly unchanged and severe injury, neuro-injury and haemorrhage biases were largely controlled for, it is not clear what caused this difference. The most obvious answer would point towards a WCE: however injury can also cause a rise in HR as described in **Chapter 1** and both tend to have an associated raised SBP.^{2,3,71,72} In this study SBP did go up, but not enough to be regarded a WCE.^{18,19} As discussed in the paper the only reasonable explanation would be that injury played at least some role.

Table 11 Descriptive statistics of injury/ age two-way analysis for heart rate (BPM)

Age	HSE		TARN	
	n	Median (IQR)	n	Median (IQR)
16-25	13687	72 (65- 80)	5152	81 (72- 92)
26-35	16291	71 (63- 78)	5957	80 (71- 90)
36-45	18482	70 (64- 77)	5628	80 (72- 90)
46-55	16262	70 (63- 76)	5564	80 (71- 89)
56-65	13618	69 (63- 77)	5842	80 (70- 88)
66-75	11789	69 (62- 77)	5645	78 (70- 88)
>76	8195	69 (62- 77)	6957	80 (70- 89)

HSE, Health survey for England; TARN, Trauma Audit and Research Network; IQR, interquartile range

Besides the main finding, there were a few additional, though largely academic findings. Although the SBP difference between these cohorts was found to be statistically significant, the real values were not particularly notable and failed to achieve the pre-agreed outcome measure threshold of 25mmHg by quite a margin. What was interesting about the two-way interaction with age was that SBP tended to be higher in younger, injured patients. As discussed in the paper, this finding had already been made in children with blunt injury where the difference was much more significant.¹³⁷ Dark, et al. showed that in children SBPs were higher than expected and the difference between actual and expected SBP increased with decreasing age. This study follows on from Dark's findings showing that this difference continues into young adult life. The authors did not give a reason for their finding, but speculated that it is likely due to injury and stress (from pain and/ or anxiety) that lead to an adrenergic response, facilitating vasoconstriction and an increase in SBP. As in this study, a small difference was also observed between injured children's HR and resting values however, the difference was much less impressive and not considered relevant. Tests measuring significance were not conducted, but instead values were considered in a clinical context using the distance of the resting values from the 50th centile of the injured values. Resting values for SBP were always below the 50th centile in contrast with resting values for HR which were on the 50th centile. Why SBP is more affected in childhood and HR in adulthood is not clear and falls beyond the scope of the study objectives.

Table 12 Descriptive statistics of injury/ age two-way analysis for systolic blood pressure (mmHg)

Age	HSE		TARN	
	n	Median (IQR)	n	Median (IQR)
16-25	13710	124 (115- 132)	5173	130 (120- 141)
26-35	16306	124 (114- 320)	5971	130 (120- 152)
36-45	18486	125 (117- 135)	5636	130 (120- 141)
46-55	16253	132 (122- 143)	5577	134 (120- 150)
56-65	13598	139 (115- 127)	5852	140 (122- 156)
66-75	11699	144 (131- 159)	5658	146 (129- 164)
>76	8121	147 (133- 164)	6962	150 (131- 171)

HSE, Health survey for England; TARN, Trauma Audit and Research Network; IQR, interquartile range

Another finding was that older patients' SBPs were largely unaffected by injury. It had already been discussed in **Chapter 1** that with increasing age, BP increases and sympathetic responsiveness decreases.^{2,41} Whatever the physiological reasoning may be, moderately injured older patients' SBPs seemed to be affected no more than someone of a similar age who had no injury at all. The key point here is that in older patients with suspected moderate injury, SBP variation from what is expected in uninjured patients should prompt an evaluation for occult causes such as haemorrhage or CNS-injury. In order to evaluate the SBP in trauma accurately, an appreciation of the physiologically higher SBP in normal older patients is needed (age over 56, median SBP of 140mmHg; age over 76, median SBP of 150mmHg; **Table 12**). With these higher values in mind, a text-book-normal SBP of 120 mm Hg might represent hypotension in the elderly and it is easy to see why the elderly are often undertriaged.^{24,109}

Immobilisation did not seem to make any real difference to either HR or SBP. Although the effect of full immobilisation on SBP was statistically significant the difference in any age group was no more than a median of 7mmHg (**Table 13**), not enough to trigger the outcome measure. This finding strengthens those from Chapter 2 which showed immobilisation's lack of effect on HR, SBP and RR in an experimental study. It would be interesting to know whether a prospective design would yield a different finding although that looks unlikely. The effect of immobilisation was not affected by age.

Table 13 Descriptive statistics of immobilisation/ age two-way analysis for systolic blood pressure (mmHg)

Age	Non-immobilised		Immobilised	
	n	Median (IQR)	n	Median (IQR)
16-25	4390	130 (120- 140)	377	131 (120- 145)
26-35	5283	130 (120- 153)	287	135 (123- 150)
36-45	5093	130 (119- 140)	235	135 (120- 148)
46-55	5126	133 (120- 149)	199	140 (129- 153)
56-65	5529	140 (122- 156)	137	140 (129- 158)
66-75	5398	146 (129- 164)	91	145 (134- 168)
>76	6673	150 (130- 171)	81	157 (140- 178)

HSE, Health survey for England; TARN, Trauma Audit and Research Network; IQR, interquartile range

Limitations

The limitations of this study are those of a case-control design. As a case-control design's main use is hypothesis formulation it does not result in a definitive answer as a prospective or another type of observational study would have done. The two main issues with case-control designs are confounding variables and bias. A confounding variable is a variable which would be related to both the dependent (TARN or full immobilisation) and independent (HSE or no immobilisation) variables, although not always visible from the data due to the restrictions of a retrospective design. The most common confounding variables in case-control designs tend to be age and gender. In this study age was controlled for by including it in a two-way design. Gender was well matched for the injury variable (TARN vs. HSE) but less so for the immobilisation variable (full vs. none). The non-immobilised group had just under 30% male subjects less than the full mobilisation group. As explained in **Chapter 2** HR is less likely to increase in females than males given painful stimuli.¹³³⁻¹³⁵ Therefore it could be possible that if the gender balance were more equitable in both groups that HR would at least have been lower than what was observed in the study. If in fact true, this would have meant that full immobilisation is associated with lower HRs than no immobilisation. As the study from **Chapter 2** showed no difference with nearly four times more female subjects, it is very likely that gender has no significant interaction with immobilisation. This finding was not specifically tested though in either study.

Sampling bias relates to both groups included in a case-control design. As patients required admission to be entered into the TARN database at the time of sampling, not all injuries were included. A large number of patients with upper limb and below-knee injuries get discharged from the ED and would thus not be represented in this sample. It may be argued that this group were less likely to have any significant physiological derangements; hence the early discharge despite similar injuries, although this was beyond the scope of this study. Similarly the HSE database only contains data of consenting participants. For instance, excessive alcohol use, a well-known cause of injury,¹⁴⁴ is likely to have been underrepresented in this sample. As alcohol tends to increase HR and SBP, this may be an additional confounding variable to investigate in future research.¹⁴⁵⁻¹⁴⁷ A well-designed prospective study would be able to follow up on the findings of this study whilst controlling for confounding variables and bias.

This study not only looked for a statistically significant effect, but also looked for a clinically relevant one. Outcome measures were chosen to represent the lowest thresholds to diagnose a WCE. However, the findings of the study seem to point to an anxiety-injury co-effect and therefore setting outcome measures to indicate WCE only would be flawed. In **Chapter 2** outcome measures were 10BPM for HR and 7.5mmHg for SBP; both an a priori decision made by the authors as acceptable thresholds to indicate a clinically relevant difference. In retrospect it seems that these may have been appropriate for this study in the original design despite not making a difference to the eventual interpretation of the data.

Chapter conclusion

This study has shown that HR in a cohort of patients with minor injuries is 10BPM higher than an uninjured one. This finding was consistent throughout all age groups. As a SBP effect is absent, it is likely that the WCE effect is only partly responsible and that minor injuries may also have contributed to the effect. Further research is needed to clarify this point. Spinal immobilisation was once again shown to have no real effect on vital signs, even in this cohort of patients with real injuries. This finding validates the findings from **Chapter 2** regarding spinal immobilisation and vital signs in an experimental group.

Chapter 4

Ambulance transport and vital signs

Reference

Bruijns SR, Guly HR, Wallis LA. Vital signs during and following ambulance transfer. Eur J Emerg Med. 2013 Apr 20. [Epub ahead of print] doi:10.1097/MEJ.0b013e32836188b4

Declaration of author

In the case of Chapter 4, the nature and extent contribution to the work was the following:

- **Nature of contribution:** SRB and HRG came up with the original idea; SRB did the majority of planning, wrote the first and subsequent drafts of the proposal, collected the data, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript and this chapter and is the corresponding author and guarantor of the publication; HRG and LAW contributed to the proposal, manuscript and chapter
- **Extent of contribution:** SRB: 85%; HRG: 10%; LAW: 5%

The following co-authors contributed to the work

1. Prof Lee A Wallis
2. Dr Henry R Guly



Signed: Stevan R Bruijns

Declaration by co-authors

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other author of the publication according these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from date indicated below

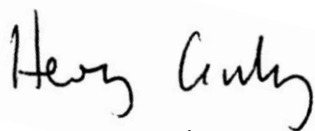
Location of stored data: Raw data are stored within a password protected database at Plymouth Hospitals NHS Trust, Plymouth, United Kingdom.



Prof Lee A. Wallis

15 July 2013

Date



Dr Henry R. Guly

15 July 2013

Date

Main findings

- Transport has a negligible effect on HR
- SBP increases from prehospital to ED triage although the effect is small
- This small effect may be attenuated by the presence of tissue injury

Argument for conducting study

It was shown in **Chapter 3** that a difference exists between a minor injured and an uninjured group, but that this difference is small and likely due to a combination of injury and anxiety factors. With this finding in mind, attention is now turned to the effect of transportation on vital signs. As described in **Chapter 1**, transport has been shown to increase adrenergic output and in normal volunteers this affected vital signs significantly.^{20,22,96} It is also known that the adrenergic effects resulting during experimental transport can be attenuated by the use of midazolam, an anxiolytic, suggesting that the effect is most likely due to anxiety related to the travel.⁹⁷ Following an extensive search of the literature only one paper could be found though that tested the effects of transport in an actual patient group.²¹ Weber, et al. evaluated the effects of transport in patients with a suspected diagnosis of ACS. The premise of that paper was that the catecholamines released due to transport might have a deleterious effect on patients with ACS. The main difference between this study and the experimental studies was that this study showed an increase in adrenergic outflow that did not translate into a significant effect on vital signs. As a single paper, the findings require validation in other settings. In particular no study appears to have been done including trauma patients. In early trauma care, vital signs, despite their poor accuracy, are seen as important markers of injury severity. If transport had an effect on vital signs similar to what was seen in the experimental studies, then clinicians will have to consider this, when making a judgement on what the vital signs represent following ambulance transport. Given that vital signs were affected by transport anxiety in the experimental models, it is very likely that the findings from Weber's paper in fact show that tissue injury (from ACS) attenuates the anxiety effect. Since injury would be part of the pathology complex of most transported trauma patients, this may also be the case where trauma is considered.

Aim

To establish whether a difference exists between the HR, SBP and RR of patients with non-haemorrhagic, traumatic injury (minimally and moderately-injured), measured during ambulance transport compared to the ED.

Objectives

1. To evaluate the difference between the HR, SBP and RR of patients during transport and on arrival in the ED
2. To evaluate the difference between the HR, SBP and RR of minimally injured patients during transport and on arrival in the ED
3. To evaluate the difference between the HR, SBP and RR of moderately injured patients during transport and on arrival in the ED
4. To compare the ED minus prehospital differences between the minimally and moderately-injured groups

A copy of the published paper follows on the next three pages

Vital signs during and following ambulance transfer

Stevan R. Bruijns^a, Henry R. Guly^b and Lee A. Wallis^a

The aim of this study was to compare vital signs of minimally injured and moderately injured patients during ambulance transport and subsequent emergency department (ED) assessment. We carried out a retrospective chart review. Patients were divided into two groups: minimally injured patients with neck pain (group 1) and moderately injured patients with a closed ankle or wrist fracture (group 2). The Wilcoxon signed-rank test was used to compare vital signs within groups during transport and ED assessment. Groups 1 and 2 included 90 and 118 patients, respectively. In group 1, systolic blood pressure was significantly lower ($P=0.001$, median difference 8 mmHg) and heart rate was significantly higher ($P<0.01$, median difference 3 beats/min) during transport than during ED assessment. There was no significant difference in respiratory rate in group 1 or any of the vital signs in group 2. We conclude that transport anxiety has minimal

effect on vital signs. In trauma, clinicians should exclude tissue injury before attributing increased systolic blood pressure or heart rate to anxiety. *European Journal of Emergency Medicine* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: ambulances, anxiety, emergencies, immobilization, pain, trauma, vital signs

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Introduction

Vital signs are used extensively to make inferences about the haemodynamic status of patients and to make management decisions or predict resources and outcome during trauma care [1]. However, the literature suggests that they do not follow the patterns attributed to them in popular trauma texts [2]. The main conditions purported to affect vital signs in trauma are haemorrhage, pain, anxiety and tissue, spine, and head and chest injury [1,3]. Consequently, interpretation of vital signs can be challenging as two or more of these may coexist. Tissue injury causes tachycardia and hypertension because of increased sympathetic vasoconstrictor tone, attenuating the initial vagal response contributed to significant haemorrhage only [3]. Although pain is considered as a cause for deranged vital signs, there is currently little evidence to support this [4]. Anxiety, however, can increase blood pressure in a clinical setting (white-coat effect) [5].

Ambulance transport may be associated with changes in vital signs, probably through anxiety. Witzel [6] described a significant increase in heart rate (HR) and mean arterial pressure with higher transfer speeds in healthy individuals. However, Weber *et al.* [7] found that HR was unaffected despite significant adrenergic output during transport of suspected acute coronary syndrome, suggesting that a difference may exist between uninjured individuals and patients with actual tissue injury.

The authors could find no study that specifically related to vital sign changes during transport in a trauma setting. If transport has an effect on the vital signs of trauma patients, knowledge of the magnitude of this may prove

useful during assessment of trauma patients once they have arrived in the emergency department (ED).

This study aimed to investigate whether a difference exists between the HR, systolic blood pressure (SBP) and respiratory rate (RR) of patients with nonhaemorrhagic, traumatic injury (minimally and moderately injured), measured during ambulance transport and in the ED. Another objective was to compare the ED minus prehospital differences between the minimally injured and moderately injured groups.

Materials and methods

A chart review was carried out for the period between February 2011 and May 2012 for patients attending the ED of Derriford Hospital (Plymouth, UK). Individuals were eligible if transported to the ED by ambulance on a stretcher and a HR, SBP and RR were documented both during transport (first measurement logged on the ambulance report form during transport) and on arrival at the ED (recorded within 10 min of arrival at triage). A 506-N3 Vitalcare (Criticare Systems Inc., Waukesha, Wisconsin, USA) was used for ED recordings and ambulance recordings were completed either manually or using an Ortivus-Mobimed Unit (Ortivus, Danderyd, Sweden). RR was measured manually. Discharge diagnoses from the ED's electronic database were used to refine eligibility for the groups as follows: for the minimally injured group, individuals who required spinal immobilization for transfer and a discharge diagnosis of neck sprain, and for the moderately injured group, individuals with a discharge diagnosis of a closed wrist or ankle fracture (no spinal

immobilization). Exclusion criteria were additional injuries other than minor injury to the trunk, head or spine (Abbreviated Injury Scale 1) [8]; minor-to-moderate injury to the upper or lower limbs (Abbreviated Injury Scale 1–2); intravenous analgesia or fluids administered prehospital; regular medication including chronotropic drugs; or an organic cause for injury (i.e. syncope). This study received ethical approval through the NHS South West 1 Research Ethics Committee (10/H0203/24), UK, and the University of Cape Town Research Ethics Committee (014/2010), South Africa.

Data analysis was carried out using SPSS version 19 (IBM, Armonk, New York, USA). As data were not normally distributed, median and interquartile ranges (quartile 1–3) were used to describe it. Prehospital and ED data were compared using a Wilcoxon signed-rank test [9]. A Mann–Whitney *U*-test was used to compare the two groups with respect to the difference (Δ) between ED and prehospital measurements [9]. This was done to determine whether the HR, SBP and RR differences between ED and prehospital were any different between the two groups, given the differences in group characteristics. A *P*-value of less than 0.05 was considered statistically significant throughout.

Clinically significant changes were defined, *a priori*, as a median difference of at least 10 beats/min, 7.5 mmHg and 2.5 breaths/min for HR, SBP and RR, respectively. To power the study to 80% ($\alpha = 0.05$), 52 individuals were required for each group. The number required was doubled to 208 individuals to ensure that at least 52 individuals were enrolled in each group and to account for the retrospective design, accommodating missing data points and caseload differences.

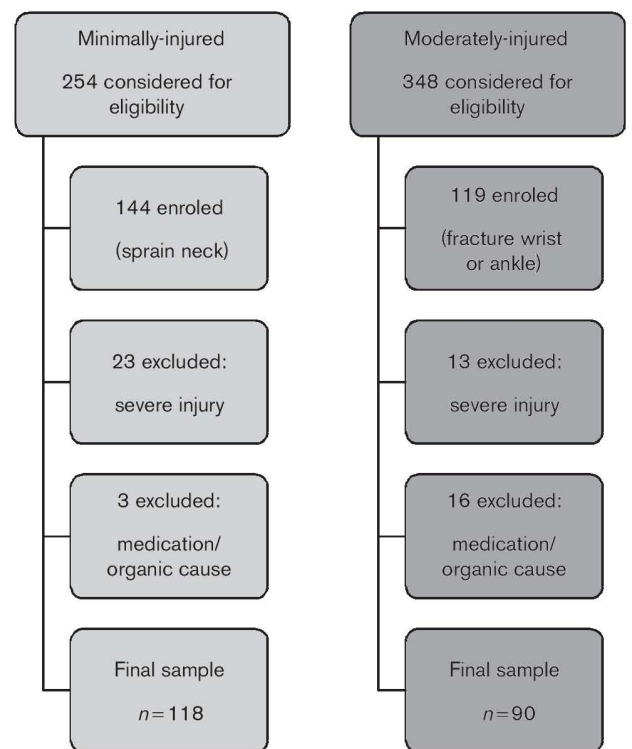
Results

Figure 1 presents the selection process. The overall median age of the patients was 45 years (31 and 62 years for minimally injured and moderately injured individuals, respectively, $P < 0.001$). There were 85 (41%) male patients [44/118 (47%) and 30/90 (33%) for minimally injured and moderately injured individuals, respectively].

Table 1 presents the results. Overall, SBP transport was statistically significantly lower than SBP ED. HR transport was significantly higher than HR ED. Neither difference was clinically significant. For minimally injured individuals, SBP transport was significantly lower than SBP ED and the median difference of 8 mmHg was considered clinically significant. HR transport was statistically significantly higher than HR ED, but this was not clinically significant. There were no significant differences between the RR transport and RR ED in any group. There were also no significant differences between transport and ED vital signs in the moderately injured group.

The Mann–Whitney *U*-test showed no difference between the minimally injured and the moderately injured

Fig. 1



Selection of the study participants.

Table 1 Descriptive statistics of vital signs measured during transportation and in the emergency department

	Transport		ED		<i>P</i> -value
	Median	IQR	Median	IQR	
Full sample					
SBP (mmHg)	133	120–149	140	126–152	<0.001
HR (BPM)	79	69–89	76	66–87	0.001
RR (bpm)	16	16–18	16	16–18	0.74
Minimal-injury group					
SBP (mmHg)	128	120–143	136	122–149	0.001
HR (BPM)	77	67–90	74	65–85	<0.01
RR (bpm)	16	16–18	16	16–18	0.23
Moderate-injury group					
SBP (mmHg)	137	120–158	143	129–157	0.08
HR (BPM)	80	72–88	78	70–88	0.06
RR (bpm)	16	16–18	17	16–19	0.44

P-value is for the Wilcoxon signed-rank test.

BPM, beats/min; bpm, breaths/min; ED, emergency department; HR, heart rate; IQR, interquartile range (quartile 1–3); RR, respiratory rate; SBP, systolic blood pressure.

groups for Δ HR, Δ SBP or Δ RR (0.3, 0.52 and 0.09, respectively).

Discussion

A transport-specific effect was not observed for SBP. This study showed that the SBP was significantly higher at ED triage rather than during ambulance transport.

This occurred only in minimally injured individuals but not in moderately injured individuals. An explanation for this finding may relate to the fact that the moderately injured individuals in the ankle/wrist fracture group suffered greater tissue injury than the individuals with neck sprain. As vasoconstrictor tone increases with increased tissue injury, any sympathetic drive attributable to anxiety would simply be attenuated and therefore less visible clinically [3]. As other causes that could influence vital signs were largely controlled for, and immobilization has been shown not to affect vital signs [10], the increase observed in minimally injured individuals at ED triage was likely because of mild anxiety (or a relative white-coat effect). Despite being clinically significant, this increase was modest at best.

HR transport was statistically significantly higher than HR ED only for minimally injured patients, but the median difference (3 beats/min) was not clinically significant. Witzel [6] showed that HR increased with associated faster ambulance transport of healthy, uninjured volunteers and suggested an anxiety as the cause. However, no such difference was observed in this study in the moderately injured group. This fits with Weber's findings in an acute coronary syndrome population (tissue injury through ischaemia), which showed a nonsignificant change in HR despite increased adrenergic output during transport [7]. As with SBP, the transport effect observed appeared either negligible or absent.

None of the differences observed in one group were significantly different from those observed in the other group for any of the vital signs. This finding suggests that the cause for any of the respective differences observed was also not different and that at least with respect to the difference between ED triage and transport vital signs, both groups were similar.

This study attempted to control for potential illness, medication, intravenous fluids, haemorrhage, spinal and head injury bias by intentionally not including any trauma associated with these. Poor note keeping rendered many individuals ineligible for enrolment and is a limitation of a retrospective design. Ideally, additional prehospital data points with associated timings would have provided a more complete data set for analysis. Measurement bias may have also played a role, given the different measuring instruments used. Although appropriately powered to address the study objectives, a larger sample would have allowed analysis of the effect of age as a separate interaction

variable. As both the transport and ED environments are considered stressful, inclusion of a baseline, at-rest phase would have been useful. Inclusion of such a phase, given the retrospective design, was not practical but should be considered in a future prospective study.

Conclusion

Transport had a negligible effect on vital signs. The effect of anxiety associated with trauma appeared to be relevant only with minimal tissue injury (such as a neck sprain) and then predominantly in the ED. Even then, the effect was minimal; for SBP, it only just satisfied our definition of clinical importance (with an increase from transport to ED). It is important that staff, both prehospital and in the ED, should not attribute increased SBP or HR to anxiety (transport or not) as its effect seems to be negligible and this practice could result in underscoring true clinical pathology. A prospective study would be helpful to refine this paper's findings.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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Discussion of study

Methods

A retrospective cohort design was chosen as this specific design generally has the advantage of providing a useful, initial perspective of a subject not a lot is known about, which in turn then aids hypothesis formulation for future research.^{132,148} Other advantages of a retrospective design include the fact that larger sample sizes are often readily available, usually as databases. These advantages come at a price since sample selection criteria are confined to the existing data which were not collected with the study in mind, potentially resulting in selection bias. For this study the ED electronic database of Derriford Hospital (Plymouth, UK) was used to extract information about patient attendance. Although frequently used for audit and research purposes this database's main purpose is clinical record keeping and not audit or research. An initial electronic search of this database using the inclusion criteria listed provided the pre-exclusion sample. The written records were then obtained in order to refine the sample. Data source quality from the written record proved variable, with absent vital sign recording resulting in the largest proportion of excluded subjects. The resulting sample was followed by further exclusions described in the paper. This process is graphically demonstrated in figure 1 in the paper. Regarding drug exclusions, it was not possible to exclude oral analgesia. It was felt that the oral route and doses used prehospital were unlikely to have had much of a systemic effect.¹³⁶ Chronotropic drugs excluded included: alpha-, beta- and calcium channel blockers, digoxin and also beta-agonists (such as salbutamol).

Neck sprain, as a minor injury often transported by ambulance, was the ideal choice for the minimally injured group. Current practice recommends that, as a precaution, patients with cervical spine tenderness following injury are immobilised and transported to the ED for assessment.^{4,5} However, only 1 to 2% of these patients will turn out to have a clinically significant cervical spine injury.^{149,150} For the second, moderately injured group, it was decided to include simple ankle and wrist fractures as the primary diagnosis. Both had to be no greater than AIS 2 injuries in order to avoid the risk of features such as haemorrhage confounding the vital signs. As spinal immobilisation was not shown to have a relevant effect on vital signs (**Chapters 2 and 4**) its inclusion in the minimally injured group was not viewed as a confounder. Subjects from the moderately injured group were not immobilised as evaluation of the database showed that given the nature of the inclusion criteria for this group, immobilisation was not commonly used during transport. For continuity's sake, the

small number of subjects that were transported with spinal immobilisation and a diagnosis of wrist or ankle fracture were not included. Subsequently these inclusion criteria were used to interrogate the ED electronic database whilst exclusion was done by hand following a review of each subject's actual records.

As described in the paper, data were found not to be normally distributed, hence the use of non-parametric analysis. The dependent Wilcoxon signed-rank test was therefore used.¹³²

A dependent test describes a repeated measures design where the earlier measurements for a subject are compared with later measurements of the same subject. The benefit of this is that each subject also serves as its own baseline. This is the reason why the two groups could be combined and an analysis be performed on the full sample despite the groups being drawn from different injury severity populations. The signed-rank test is, in fact, not all that different from the dependent t-test (its parametric alternative) in so far that it is based on the differences between two dependent measurements. As with other non-parametric tests ranking is required and in the signed-rank test this applies to the difference between two measurements for each subject.

The Mann-Whitney U test was used to compare the respective HR, SBP and RR differences (or delta, Δ) between the minimally and moderately injured groups. This was a secondary objective in the paper. The reason the groups were not compared outright was because each group's make up differed with respect to age and gender predominance. An outright comparison would have been confounded by these (i.e. higher SBPs in the older, moderately injured group). By isolating the Δ HR, Δ SBP and Δ RR and comparing those between the groups, the absolute HR, SBP and RR values became less relevant and comparison was less biased.

The sample size calculation is similar to the one described in **Chapter 2**. The only difference was that for this study the resulting sample required was doubled to compensate for expected retrospective design complications as described above. Similar to the study from **Chapter 2**, SDs were drawn from the same studies evaluating the effect of pain or transport on vital signs.^{82,83,85,121} Outcome measures were chosen in a similar fashion as was done in **Chapter 2**. The outcome measures were used to evaluate the Δ effect of transport on vital signs with Δ values that met outcome measures denoted as clinically significant. Clinical significance therefore differed from statistical significance, the latter which is mainly dependent on sample size. The larger a sample the stronger the statistical test's power to determine a difference becomes. Depending on what is evaluated, the difference is not

necessarily a useful answer in a clinical setting. For example in this study a larger sample size would have resulted in smaller Δ -values being described as statistically significant and vice versa. It is therefore important to interpret statistical significance in the light of an expected outcome measure or effect size, in order to ensure the result also conveys clinically significant information.

Results

The main finding was that SBP increased significantly from prehospital to ED both overall and in the minimally injured group. From table 1 in the paper it is shown that the SBP also increased in the moderately injured group although this was not found to be significant. If anxiety were indeed the responsible confounder, then this finding would suggest that anxiety was not due to transport anxiety, but rather an ED WCE. The outcome measure for SBP was satisfied only just for the minimally injured group. Tissue injury may also have played a role (through attenuating the adrenergic response that resulted from anxiety) and, perhaps, the difference in age between the groups (the minimally injured group was younger by half than the moderately injured group). In **Chapter 3** it was shown that younger subjects tend to be more prone to a WCE. SBP values in younger subjects in that study were found to be more reactive to injury and anxiety than of that seen in older subjects. However, the difference between injury SBP and non-injury SBP at any age was not clinically relevant at any point. It is therefore likely that the increase in SBP seen in the minimally injured group in this study had, at least in some respect, to do with this group being about half the age of the moderately injured group.

An additional finding was that the Δ HR, Δ SBP and Δ RR between the two groups showed no significant difference. This suggests that any difference that occurred in one group was no different from that seen in the other group. This casts the clinically relevant increase in SBP seen in the minimally injured group in a slightly different light, as statistically this significant difference is no different from the non-relevant increase seen in the moderately injured group. This would suggest that the same process that caused the increase in the minimally injured group also caused it in the moderately injured group. Age, gender and injury severity were different for each group so these were less likely to have a major impact. The only constant applicable to both was the location (prehospital versus ED). It is known from prior research that transport causes adrenergic outflow due to anxiety. Perhaps in trauma adrenergic outflow due to transport anxiety increases relative to the tissue injury attenuating effect described earlier, resulting in a relative *white-coat-like-effect* on arrival in

the ED (to satisfy the definition of a true WCE, HR increase should be greater than 10BPM and a SBP increase greater than 25mmHg).^{18,19} As already stated in the study conducted in **Chapter 3** this effect was mainly observed in younger subjects. More importantly however, was that overall the effect was simply not clinically relevant. Age and injury severity probably played only a minor role.

Limitations

The use of different measuring devices was a limitation. Although no data is specifically known about the comparative accuracy of the 506-N3 Vitalcare and Ortivus-Mobimed in measuring HR and SBP, it is known that some degree of variability exists between devices made by different manufacturers and there are probably differences between different devices of the same type.¹⁵¹ Digital devices such as these tend to have accuracy on par with mercury sphygmomanometers (the reference standard).¹⁵¹ This is because electronic devices use oscillometrics to derive the SBP from the precise mean arterial pressure measurements. The manufacturer for the 506-N3 vitalcare claims accuracy within 2% (or 2mmHg, whichever is greatest), whilst no data is known for the Ortivus-Mobimed.¹⁵² The manual SBP readings were done using an aneroid sphygmomanometer (the mercury type is no longer used by the National Health Service). Aneroid devices make use of air and needs frequent calibration to maintain accuracy. Of the three types, these are the least accurate.¹⁵¹ Ideally use of the same device and operator would yield consistent results although this was not feasible in the retrospective design. In real life, when a patient moves from the ambulance to the ED or from the ED to a ward, the BP measurements taken in both locations are assumed to be equivalent, even though they are taken with different instruments.

In planning this study, we had not anticipated the wide difference in age between the two groups and it might have been useful if the two groups had a similar age distribution. However, given the way that the statistics were employed to compare the difference (Δ) in prehospital and ED vital signs between the minimally and moderately-injured groups and not the absolute values, this seemed to make little difference and perhaps even suggested that age had little influence on transport anxiety related vital sign changes.

Additional data points pre-transport and baseline (at rest) may perhaps have been useful to make further sense from this study although this could have made interpretation more complex than the simple design eventually employed. Although pre-transport levels were

originally included for sampling, documentation of it was so poor that collection had to be abandoned. It is likely that because subjects were minimally injured, attention were only given to measuring vital signs once the subject was packaged for transport or transport was already in progress. It is likely that pre-transport measurements would have been more forthcoming in cases of severe injury. Even so, when the results from **Chapter 3** are considered: that the HR difference between a moderately injured and non-injured cohort were only 10BPM and that the SBP difference was not clinically relevant, it can be inferred that even if pre-transport HR and SBP were different it is unlikely that this would have been a considerable difference. Further research is needed to confirm the findings in this study.

Chapter conclusion

If anxiety over ambulance transport affects the vital signs of injured patients, it does so no more than ED WCE. The variable with the biggest change from prehospital to ED was SBP which showed, contrary to what was anticipated, an increase from prehospital to ED. The overall increase observed was however not clinically relevant. The effect on HR and RR were negligible. In addition to an anxiety effect, age and injury severity potentially have a lesser effect. Further research based on these findings would be a sensible way of confirming the findings. A prospective cohort design should theoretically be able to control for the limitations and bias of the retrospective design. All in all, ambulance transport and the anxiety associated with it do not seem to have any meaningful effect on vital signs in the trauma setting.

Given the findings from **Chapters 2 to 4** as well as the known confounders discussed in **Chapter 1** (age, PMCs, etc.), the next two chapters will focus on novel ways to potentially improve the accuracy of vital signs in predicting outcome. **Chapter 5** looks at the prognostic value of the differences between prehospital and ED vital signs and **Chapter 6** at the prognostic value of mathematical combinations of vital signs in relation to each other and age.

Chapter 5

The difference between emergency department and pre-hospital vital signs as indicators of mortality

Reference

Bruijns SR, Guly HR, Bouamra O, Lecky F, Wallis LA. The value of the difference between ED and prehospital vital signs in predicting outcome in trauma. Emerg Med J. 2013 Apr 24. [Epub ahead of print] doi:10.1136/emmermed-2012-202271

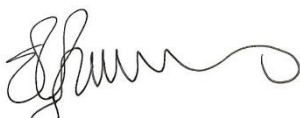
Declaration of author

In the case of Chapter 5, the nature and extent contribution to the work was the following:

- **Nature of contribution:** SRB and HRG came up with the original idea; SRB did the majority of planning, wrote the first and subsequent drafts of the proposal, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript and this chapter and is the corresponding author and guarantor of the publication; HRG and LAW contributed to the proposal, manuscript and chapter; OB contributed to the statistical analysis and manuscript; FL contributed to the planning and manuscript
- **Extent of contribution:** SRB: 75%; HRG: 10%; LAW: 5%; OB: 5%; FL: 5%

The following co-authors contributed to the work

1. Prof Lee A Wallis
2. Dr Henry R Guly



Signed: Stevan R Bruijns

Declaration by co-authors

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other author of the publication according these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from date indicated below

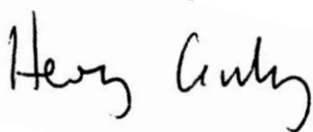
Location of stored data: Raw data are stored with the Trauma Audit and Research Network. Manipulated data are stored within a password protected database at Plymouth Hospitals NHS Trust, Plymouth, United Kingdom.



Prof Lee A. Wallis

15 July 2013

Date



Dr Henry R. Guly

15 July 2013

Date

Main findings

- In blunt trauma, in patients without central nervous system (CNS) injury, a SBP that is lower, or a RR that is higher in the ED than prehospital predicts 48 hour mortality
- In blunt injury of moderate severity in patients without CNS injury, an increase in the SI from prehospital to ED predicts 48 hour mortality
- In blunt trauma in patients without CNS injury, an increase in HR from prehospital to ED has no value in predicting outcome.

Argument for conducting study

Chapters 2 to 4 have shown that spinal immobilisation, anxiety and transport anxiety do not appear to have any clinically relevant effect on vital signs. This adds to the evidence that pain also has a minimal effect.⁸²⁻⁸⁵ The main effect on vital signs thus appears to relate to the type of injury itself, the age of the patient and the presence of PMCs.^{4,17-25} Since blunt injury is more common than penetrating injury as well as more likely to be occult, early recognition of deterioration is paramount as this will guide early management when injury severity is still unclear early on.^{4,110} Age and the presence of PMCs will certainly have an effect on vital signs' response to injury, but since both of these are constants, untreated injury would be the only variable that may have a real-time effect on vital signs (i.e. deterioration, no change or improvement). As such, if injury is severe enough to result in general deterioration from scene to hospital, then perhaps the difference between initial vital sign measurements prehospital and subsequent measurements in the ED would give an indication of deterioration. Interestingly this hypothesis has not been thoroughly evaluated in the literature. Only three papers were found that compared prehospital vital signs with those in the ED in order to predict outcome.^{110,117,118} The vital signs evaluated were the SI and SBP (HR and RR have not been looked at). Cannon et al. evaluated an ED-prehospital difference threshold (delta, Δ), but this was only done for the SI.¹¹⁰ The remaining two papers found an increase in mortality if ED-SBP was lower than prehospital-SBP.^{117,118} All three papers included CNS injury in their samples.^{110,117,118} Since head injury accounts for nearly half of trauma deaths,¹⁵³ these papers' findings do not reliably reflect whether their findings would apply to non-CNS injury. Poor outcome in head injury is already strongly associated with a reduced Glasgow Come Scale (GCS) even in isolation,¹⁵⁴ which effectively allows for early identification via computed tomography (CT). The question thus remains over whether a difference in vital signs in a non-CNS injury sample

would be as predictive. If so, these Δ vital sign measurements may represent a more accurate way to predict a poor outcome in the presence of non-CNS injury than absolute vital sign measurements currently do.^{9-13,34-37,39,40}

Aim

To evaluate whether the difference (Δ) between SBP, HR, RR and SI taken in the ED and prehospital can predict outcome at 48 hours post admission following non-CNS trauma

Objectives

1. To evaluate the difference between SBP, HR, RR and SI taken in the ED and prehospital and 48-hour mortality
2. To establish the threshold for the difference between SBP, HR, RR and SI taken in the ED and prehospital in predicting 48-hour mortality at 90% specificity
3. To establish the threshold for the difference between SBP, HR, RR and SI taken in the ED and prehospital in predicting 48-hour mortality at 95% specificity

A copy of the published paper follows on the next four pages

The value of the difference between ED and prehospital vital signs in predicting outcome in trauma

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ABSTRACT

Introduction Traditional vital signs are seen as an important part of trauma assessment, despite their poor predictive value in this regard.

Objective This study evaluated whether the difference between systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR) and shock index (SI) taken in the emergency department (ED) and prehospital can predict 48 h mortality postadmission following trauma.

Methods Retrospective cohort was obtained from the Trauma Audit and Research Network. Subjects were excluded if head or spinal injuries, prehospital intubation or CPR were present. Main outcome was 48 h mortality. The difference (delta, Δ) between ED and prehospital values were used as study variables (ie, $\Delta SI = SI - ED$ minus SI-prehospital). Accuracy was assessed using area under receiver operator characteristic curve (AUROC). AUROC coordinates were used to identify 95% specificity cut points and described further using sensitivity and likelihood ratios (LRs).

Results Significant AUROC statistics were revealed for ΔSBP (0.57) and ΔRR (0.56) for the full sample, ΔSBP (0.62) and ΔSI (0.65) for moderate, and ΔRR (0.6) for severe injury. Best LRs were 3.4 and 2.4 for ΔRR and ΔSI , respectively, but sensitivities were low ($\leq 26\%$). Cut point values for ΔSBP , ΔRR and ΔSI were 37 mm Hg, 8 breaths/min and 0.2, respectively.

Discussion ΔSBP and ΔRR performed best overall, but ΔSI performed best in the moderate injury group, suggesting earlier identification with ΔSI . Use of Δ values result in good rule-in of 48 h mortality and may supplement trauma treatment decisions.

INTRODUCTION

In the management of trauma patients, vital signs have traditionally been used to assess severity, guide management and review treatment response.¹ Successful resuscitation of the trauma patient depends on actions taken in the emergency department (ED), and also those taken before the patient arrives at the ED.^{2–3} One of the main aims of prehospital care is to transport trauma patients safely to the most appropriate level of care as soon as the situation allows.^{2–3} Vital signs measured in the prehospital setting form part of ED trauma team activation criteria in use internationally despite being poor at predicting mortality, and better markers of physiological disturbance are needed.^{1–4–5} The shock index (SI) has been reported as possibly such a marker.⁶ SI, or the ratio of heart rate (HR) to systolic blood pressure (SBP), is described to be a better marker than the vital signs it is made up of.⁵ According to the literature, SI indicates injury severity, need for massive transfusion, occult haemorrhage and mortality when patients are

normotensive.^{7–10} Given that roughly a quarter of trauma cases are made up of older patients this is useful since the elderly do not respond similarly to younger patients.¹¹ HR and blood pressure is shown to be largely non-predictive of severe injury in this group which is not surprising, given that in the elderly, SBP often tends to be higher and HR lower than generally expected.^{11–13} A decrease in SBP, resulting in a relative hypotension for the patient, may be considered within 'normal' limits while the HR (unable to compensate due to reduced adrenergic sensitivity) changes little from baseline.¹³ For injuries of the same severity, the elderly often require more acute interventions than the younger patient, and mortality is higher.^{11–12} In addition, research shows that trauma undertriage occurs more often in the elderly.^{11–12} The SI, which has also been researched in prehospital literature,^{8–14–15} may, therefore, potentially be an important marker in the elderly. It is important to consider that, in addition to haemorrhage, vital signs can also be affected by head, spinal and chest injury as well as pre-existing medical conditions (the latter, interestingly, independent of age).^{1–16}

It is clear that we need better measures to predict outcome and the degree of blood loss. It would seem likely that a patient with severe injuries or major blood loss will deteriorate, physiologically, with the passage of time, and we hypothesised that the difference in vital signs (including SI) between the ED and prehospital values could be used to guide triage decisions.

The aim of this study was to evaluate whether the difference between SBP, HR, respiratory rate (RR) and SI taken in the ED and prehospital can predict 48 h mortality postadmission following trauma. Patients with severe injuries are clearly more likely to have a poor outcome, but it is important to predict the unexpected poor outcomes from moderate injuries such as may occur in elderly patients.^{11–13} Therefore, in addition to evaluating outcomes for the full sample, they were also evaluated for moderate (ISS 9–15) and severe (ISS > 15) injuries.

METHODS

Setting

This was a retrospective observational study using data obtained from the Trauma Audit and Research Network (TARN). TARN is the largest trauma database in Europe, and collects data related to trauma patients from a group of collaborative hospitals in England and Wales. This study was approved by the research ethics committee of the University of Cape Town, South Africa (reference 014/2010). It is reported in accordance with the guidelines set by

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Original article

Table 1 Breakdown of outliers removed

	N	%
Initial sample	29 935	
Outliers (z>3)	1662	5.6
Δ RR	594	2
Δ HR	531	1.8
Δ SI	447	1.5
Δ SBP	359	1.2
Age	1	0
Final sample	28 273	

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SI, shock index.

the *Strengthening the reporting of observational studies in epidemiology* (STROBE) statement.

Sample

Data from 29 935 cases were extracted from the TARN database for the period 1996–2006. Subjects were included if they were older than 16 years of age, and their HR, RR and SBP were collected both prehospital and in the ED. Because of the effects of head and spinal cord injury on vital signs, subjects were excluded if they had head or spinal injuries other than minor. Unknown injuries, or patients who required either prehospital intubation or CPR were also excluded. Minor head or spine injury was described as injuries with an Abbreviated Injury Scale (AIS) score of no more than 1.¹⁷

The main outcome was 48 h mortality. The difference (delta, Δ) between ED values and prehospital values were used as the main study variables to be evaluated against this outcome (ie, Δ SBP=SBP-ED minus SBP-prehospital). SI was calculated as HR/SBP. As per convention, moderate injury severity was described as an ISS of 9–15 and severe injury as an ISS greater than 15.

Management of bias

Inspection of the data sample for bias revealed the likely presence of extreme outliers for age, Δ SBP, Δ HR, Δ RR and Δ SI, which was confirmed using z-scores. Z-scores standardises a dataset by expressing it as a distribution with a mean of 0 and SD of 1.^{18 19} It follows that in terms of SDs, 5% of data will be

in excess of 1.96, 1% in excess of 2.58, but none greater than 3.29 (any value in excess of 3.29 would essentially be considered an outlier).^{18 19} Data were inspected to determine a cause, and it was found that outliers were most likely due to data and sampling errors and, therefore, illegitimate (example: HR-prehospital=1 beat/min, but with SBP-prehospital=129 mm Hg, HR-ED=96 beats/min and ISS=11). Transformation did not improve the sample, and truncation was considered inappropriate.¹⁹ Therefore, cases containing outliers were removed from the sample (using z-scores greater than three as threshold as per convention)^{18 19} in order to reduce any inflated error variance, reduced statistical power and bias that would result if it were retained.

Analysis

Data analysis was performed using SPSS V.19. Given that data were not normally distributed, median and interquartile range were used to describe age, prehospital time and Δ values. Prehospital time was calculated as scene time plus travel time to ED. Gender and injury severity (moderate and severe) were also described. The sample was described in terms of the full sample and for 48 h outcome (survival or death). A Mann–Whitney U test was performed to describe the difference between 48 h survival and mortality.

Accuracy of Δ values was assessed using area under receiver operator characteristic curve (AUROC) statistics for the full sample as well as for moderate and severe injury severity. AUROC coordinates were used to identify the nearest Δ variable values at the 90% and 95% specificity cut points. These were then further described in terms of sensitivity and positive likelihood ratios (LRs). Significance was indicated throughout as an α level of less than 0.05 and 95% confidence limits were given for LRs.

RESULTS

Outliers were identified and removed before the main analysis started, and are detailed in table 1. Descriptive statistics are summarised in table 2. When 48 h survival was compared with mortality, only age and Δ RR values differed significantly ($p<0.001$ and $p=0.02$, respectively, Mann–Whitney U test). There were no missing data points. The sample included more males than females and overall mortality was 0.4%. The mortality rate for the minor injury severity (ISS<9) category was 0.15%, which

Table 2 Descriptive statistics

	Full sample		48 h outcome			
			48 h survival		48 h mortality	
n (% of all)	28 273		28 166 (99.6)		107 (0.4)	
Male (%)	16 214 (57)		16 166 (99.7)		48 (0.3)	
Moderate (ISS 9–15) (%)	14 892 (53)		14 850 (99.7)		42 (0.3)	
Severe (ISS>15) (%)	1510 (5)		1462 (97)		48 (3)	
Penetrating injury (%)	896 (3)		890 (99.3)		6 (0.7)	
	Median	IQR	Median	IQR	Median	IQR
Prehospital time (min)	20	14–29	21:02	14–31	24:57	17–34
Age	49	31–67	49	31–67	79	59–87
Δ SBP (mm Hg)	2	10–21	2	–10–21	–4	–20–16
Δ HR (beats/min)	–2	–10–5	–2	–10–5	–2	–9–7
Δ RR (breaths/min)	0	–2–2	0	–2–2	0	–2–6
Δ SI	–0.03	–0.15–0.05	–0.03	–0.14–0.05	–0.03	–0.16–0.12

HR, heart rate; Min, minutes; RR, respiratory rate; SBP, systolic blood pressure; SI, shock index.

Table 3 Area under receiver operator characteristic curve statistics for 48 h mortality

	All			Moderate (ISS 9–15)			Severe (ISS>15)		
	AUROC	p Value	95% CI	AUROC	p Value	95% CI	AUROC	p Value	95% CI
Δ SBP	0.57	<0.01	0.52 to 0.63	0.6	0.03	0.51 to 0.69	0.55	0.21	0.46 to 0.65
Δ RR	0.56	0.02	0.50 to 0.63	0.52	0.6	0.43 to 0.62	0.59	0.04	0.5 to 0.67
Δ SI	0.53	0.22	0.47 to 0.59	0.62	<0.01	0.53 to 0.71	0.51	0.77	0.42 to 0.61
Δ HR	0.51	0.5	0.46 to 0.6	0.55	0.23	0.47 to 0.64	0.53	0.43	0.46 to 0.61

AUROC, area under receiver operator characteristic curve; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SI, shock index.

increased 20-fold to the severe injury category (2.9%). A longer prehospital time was not associated with a significant increase in 48 h mortality. The median age was markedly higher in those who died compared with those who survived the first 48 h ($p<0.001$).

The AUROC statistics showed that ΔSBP (area=0.57, $p<0.01$) and ΔRR (area=0.56, $p=0.02$) were the only significant predictors when the entire sample was considered. This varied from the analysis performed for the two injury severity categories. For moderate injury, ΔSI (area=0.62, $p<0.01$) and ΔSBP (area=0.6, $p=0.03$) were significant, and for severe injury, ΔRR (area=0.59, $p=0.04$) was the only significant variable. These results are described in table 3.

Accuracy statistics are described in table 4. Of note is, that positive LR for 48 h mortality were highest for ΔRR, followed by ΔSI (for both the 90% and 95% specificity cut point values). The worst performing Δ variable was ΔHR. Using the Δ variable values from the 95% specificity cut-off, mortality increased by 3.4, 2.4, 1.6 and 1.4 for ΔRR, ΔSI, ΔSBP and ΔHR, respectively, from overall mortality.

DISCUSSION

It is important that patients are assessed and vital signs measured at the scene of an injury both to assist in triaging the patient to the correct facility and to act as a baseline against which changes can be measured. When a patient arrives in the ED, a SBP that is lower, or a RR that is higher than that measured prehospital is associated with an increased risk of 48 h mortality. It should be noted that significant AUROC values were generally low which translated to low sensitivities at the high, preset specificities; indicating good rule-in, but poor rule-out value (table 4). While it may seem intuitive that a drop in SBP between 26 and 37 mm Hg should prompt intervention (table 4), this could be overlooked if the drop in SBP occurred

in a hypertensive patient, or if the prehospital values were never considered. When one reflects that the median age in the death group was nearly 80 years (an age where hypertension has a high prevalence),²⁰ a relative drop in SBP may be important not to miss; a drop in SBP from, say, 155 to 120 mm Hg may go unnoticed if the latter value is regarded as normal and no attention was paid to the higher prehospital value.¹³ It is known that a drop in SBP (even brief) contributes to an increase in intensive care stay and mortality.^{21–22} As an important predictor, it is important that emergency physicians and trauma surgeons take note of the prehospital SBP while considering the effects of age on trauma outcome as described in the introduction.

For moderate injury severity, ΔSI was highly significantly associated with 48 h mortality, while ΔSBP also performed well. This is an interesting finding as it could support SI as a useful marker of 48 h mortality in a moderately injured cohort where clinical deterioration may be unclear. It was notable that patients who died were significantly older than those who survived, validating past research already described.^{11–12} Considering accuracy statistics, ΔRR had the best overall positive LR. Essentially, 48 h mortality is 3.4 times higher if there is a rise in RR by 8 breaths/min or more. As an often ignored vital sign, this is an important finding underlining the importance of measuring RR in acute trauma care.²³ Of all the Δ variables, ΔHR never achieved AUROC significance, and its dire positive LR suggests very little utility. It is possible that the relative bradycardia seen in nearly a third of trauma cases where the SBP is less than 90 mm Hg may have played a role, although this was not specifically looked for.²⁴

There is not much literature comparing ED vital signs with prehospital signs. Cannon *et al*¹⁰ described a ΔSI value of 0.3 after observing an increase in mortality when SI increased from prehospital to ED. Mortality reported in Cannon's sample (7%)

Table 4 Accuracy statistics for cut point nearest to 90% and 95% specificity

Variable	Cut point	Specificity	95% CI	Sensitivity	95% CI	+LR	95% CI
Nearest to 90% specificity (variables ranked from highest to lowest likelihood ratio)							
Δ RR	6	89	88.9 to 89.7	26	18.0 to 35.9	2.4	1.7 to 3.4
Δ SI	0.1	90	89.7 to 90.4	20	12.9 to 29.4	2.0	1.4 to 3.0
Δ SBP*	–26	90	89.4 to 90.1	14	8.1 to 22.7	1.4	0.8 to 2.2
Δ HR	14	90	89.9 to 90.6	9	4.5 to 16.8	0.9	0.5 to 1.7
Nearest to 95% specificity (variables ranked from highest to lowest likelihood ratio)							
Δ RR	8	96	96.0 to 96.4	13	7.4 to 21.6	3.4	2.1 to 5.7
Δ SI	0.2	95	94.8 to 95.3	12	6.6 to 20.4	2.4	1.4 to 4.1
Δ SBP*	–37	95	94.7 to 95.3	8	3.8 to 15.6	1.6	0.8 to 3.1
Δ HR	21	95	94.6 to 95.1	7	3.1 to 14.4	1.4	0.7 to 2.8

*Reducing value will increase specificity.

HR, heart rate; +LR, positive likelihood ratio; RR, respiratory rate; SBP, systolic blood pressure; SI, shock index.

Original article

was higher than that of this study (0.4%). Other key differences were that this study limited mortality to 48 h (to focus on acute outcome); included all levels of severity and had a penetrating injury rate of 3%, whereas Cannon used mortality for the entire length of inpatient stay up to death or discharge, did not include minor trauma, and had a penetrating injury rate of 26%.¹⁰ Accuracy statistics were not reported specifically, but available data were sufficient to calculate a specificity of 96%, sensitivity of 20% and positive LR of 5.17 for the reported $\Delta SI > 0.3$ (in our sample, a $\Delta SI > 0.3$ would have a specificity and sensitivity of 98.5% and 3%, respectively). Two further studies were found that compared prehospital and ED data, but did so only for SBP and not as a Δ variable. Both Arbabi *et al*²⁵ and Franklin *et al*²⁶ found that mortality from blunt injury increased approximately 2.5 times if the ED-SBP was lower than the prehospital SBP compared with the other way around. As far as Δ values for HR, RR or SBP are concerned, the authors could find no references in the literature.

With regards to limitations, the short prehospital time possibly influenced results through patients accessing definitive trauma care early in the course of their injury management. This is evidence of a well-developed prehospital system, and results may, therefore, be quite different in a less developed setting. As the study was not set up to look at prehospital performance, inferences made in this regard should be done with due care. This study mainly considers blunt trauma. It is likely that Δ values may be different with a higher prevalence of penetrating injury such as seen in Cannon *et al*.¹⁰ Data collection errors in large samples such as this are always a concern; however, the authors tried to reduce this bias as much as possible through removal of outliers as described. Further research in less developed trauma care and higher penetrating injury prevalence settings is required, perhaps controlling for the effect of age. Exclusion of central nervous system (CNS) injuries due to their particular effect on vital signs, resulted in the mortality reported being much lower than expected. TARN data reported by Fuller *et al*²⁷ shows a 30 day mortality rate of 18% when head injury is present, compared with 3.5% when it is not. The small difference between mortality reported by Fuller and our paper can be explained when one considers the trimodal distribution of death in trauma (Fuller's paper reported on 30 day mortality, whereas our paper reported on 48 h mortality),^{1 27} and also the additional exclusions (unknown injuries, prehospital intubation and CPR). It would be interesting to see if these Δ values have any role in CNS injury in future research.

In summary, with the exception of ΔSI , we believe this to be the first study looking specifically at the differences between prehospital and ED vital signs and their relationship with 48 h mortality in mainly blunt trauma patients without CNS injury. Sensitivities were low even when specificity was set as low as 90% (the lowest clinically useful value the authors considered). Positive LRs for specifically ΔRR and ΔSI were reasonable (the latter proving particularly useful given its association with 48 h mortality for moderate injury severity, the proxy for well-looking patients likely to have a poor outcome). This study has shown that use of these Δ variables supplement outcome prediction. Emergency physicians and trauma surgeons should consider prehospital vital signs as part of their primary assessment, acting appropriately to negative changes. When the patient is elderly, extra vigilance should be employed and triage thresholds should be lowered.

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Contributors SRB and HRG came up with the original idea; SRB did the majority of planning, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript is the corresponding author and guarantor of the publication; HRG, LAW and FL contributed to the proposal and manuscript; OB contributed to the statistical analysis and manuscript.

Competing interests None.

Ethics approval Research Ethics Committee of the University of Cape Town, South Africa (reference 014/2010).

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement The data used in this study is available to bona fide researchers through the Trauma Audit and Research Network (<https://www.tarn.ac.uk/>).

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Discussion of study

Methods

Since the statistics used in this chapter are by far more technical than used elsewhere in the thesis, and the majority of analyses used in this chapter are also utilised in **Chapter 6**, this section will mainly expand on statistical reasoning. The discussion will include error rate, addressing bias, the central limit theorem and describing the use of area under the receiver operating curve (AUROC) and likelihood ratios.

Using a large database in order to boost the power of statistical tests through their huge sample sizes is not without problem. Errors can arise almost at every level of the data sampling and entry process, which in turn can affect the validity of the subsequent analysis and its conclusions if the error rate is high enough. The commonest types of database error that apply to the TARN database relate to source, keying, selecting and formatting errors, and data omission.¹⁵⁵ Keying and selection errors refer to data being incorrectly transcribed through mistyping or incorrect selection from input menus (e.g. 135.2 transcribed as 13.52) and account for approximately 1 in 245 of transcription errors.¹⁵⁵ A formatting error occurs when a database expects data to be entered in a specific format and this is not done correctly; for instance the date 11/12/2002 may be interpreted differently depending on whether the system is American (month placed first) or European (month placed second). As a result, the TARN has to ensure accuracy through strict internal system validation and coding regulations.¹⁵⁶ One example is a review of the number of times certain fields are completed correctly submitted by each respective contributing site. The rate for Plymouth Hospitals NHS Trust for instance is 95.1%. This means that despite all these safeguards, a 4.9% error rate still occurred which may result in a higher than expected outlier rate.

As large databases invariably have database errors, consideration should be given to seeking out these errors and to reduce them as much as possible.^{132,157} One way of looking for errors is to screen the data for outliers before analysis starts as was done in this paper. For this particular study, the likelihood of error became evident once the Δ variables were calculated. The results showed a number of nonsense results (such as the example given in the paper). To search for outliers, z-scores were employed as described in the paper to first establish and second remove outliers beyond a z-score of three standard deviations (SDs). Calculation of z-scores was discussed in **Chapter 2**. Statistically any value that exceeds 3.29

SDs would be an outlier however, convention dictates that if z-scores are used to clean up outliers a threshold of three SDs be used.

Table 14 Typical data transformations

Transformation	Correct for	Downside
Log: applying the logarithm to the data	Positive skew, unequal variances	Can't apply to zero or negative numbers
Square root: taking the square root of the data	Positive skew, unequal variances	Can't apply to negative numbers
Reciprocal: dividing 1 by each data point	Positive skew, unequal variances	Reversing size of data points can affect interpretation
Reverse score: subtract data points from the highest data point and then applying any of the above	Negative skew	Reversing size of data points can affect interpretation

Alternative options to managing outliers include transformation and truncation.¹³²

Transformation of the sample can take many forms, but essentially it involves changing the data by applying a mathematical equation to each data point. The aim of transformation is to improve the distribution of the data. Z-scores are in fact a form of transformation.

Other common transformation techniques include log, square root, reciprocal and reverse score transformation which are summarised in Error! Reference source not found..¹³² What is important about transformation is that no data are removed from the sample. Many authors however feel that use of robust parametric tests (such as the F-test in ANOVA) negates the use of transformation as these tests would perform well, given a large sample, even when the assumption of normality has been violated. This is the main message of the central limit theorem that suggests that in large samples distribution can be assumed to be normal. The downside to transformation is that results from analysed data cannot be reversed to reveal findings in familiar units. Use of the incorrect transformation technique can also have an effect on results. Truncation on the other hand is a fairly similar process to what was described earlier with z-score outlier identification, with the small difference that outliers are not removed but truncated to the highest (or lowest) score that is not an outlier.^{132,157} This essentially means that all outliers are replaced by this highest (or lowest) score. Once again the convention is to use the mean plus (or minus) three SDs to find the highest (or lowest) score. However, since the outlying data in this study sample was so clearly unlikely to be correct it was decided that removal was the most appropriate way to

deal with the outliers. Interestingly, z-score transformation and removal of outliers was not used for the samples in **Chapter 3**. Since this study did not consider mortality as a variable, identifying nonsense entries was more difficult. Instead data were rank transformed to allow the use of two-way ANOVA testing. Non-parametric statistics were used for the analysis of data in this study as with the studies described in the other chapters. However, as mentioned above, the central limit theorem suggests that given this study's large sample size, parametric statistics may also have been appropriate.^{132,158} The problem tends to be deciding when *large* is *large enough*. In addition, when deciding to apply the central limit theorem and use parametric statistics it is important to bear in mind that an incorrect decision in a too small sample may mean that the assumption that the type I error (alpha) is 0.05 would also be incorrect. Since power is dependent on alpha there would be no way to calculate this accurately and this could impact on the interpretability of the findings. Arguably a sizeable sample (such as TARN) should, at least theoretically, also suggest a high power, but this would depend on the type of analysis and sub-analysis planned. Non-parametric (or assumption-free) statistics tend to yield accurate results so long as data are not normally distributed. When data are normally distributed non-parametric statistics tend to overestimate the type II error rate, though even this reduces to almost negligible when the sample is large. As a result, use of either type of statistics would likely yield fairly similar results since parametric statistics tend to be rather robust to violations of assumptions in large samples and non-parametric statistics being only slightly less powerful than parametric tests when there are no violations in large samples. The decision to use non-parametric statistical analysis was therefore based on the finding that the smaller vital sign samples described in **Chapters 2** and **4** violated the assumption of a normal distribution. This same argument was applied to **Chapters 3** and **6** where non-parametric analysis was used.

In order to evaluate the discriminatory power of each of the Δ vital sign variables to predict 48 hour mortality, area under the receiver operator characteristic curve was employed.¹⁵⁹ Essentially a receiver operator characteristic curve (ROC) represents a graphical display of the sensitivity and specificity of a variable with a preferred outcome (death in this case) from a binary selection (survival or death), plotted for each data point to form a curve (**Figure 3**). From the figure it is clear that the data point closest to the upper left corner (indicated with a black dot; sensitivity 90% and specificity 80%) will have the highest accuracy. The value of any data point can be used as a reference and this value is then referred to as a cut-point. For example in this study we specifically chose a specificity of

95% (or 0.95) which yielded a cut-point value of -37 mmHg for SBP. Mathematically the AUROC created by all the data points can be calculated and this ranges between 0.5 and 1. The AUROC represents the probability that a randomly chosen, affected subject (i.e. died within 48 hours) is correctly ranked with greater suspicion than a randomly chosen unaffected subject (i.e. survived beyond 48 hours). Values closer to 0.5 suggest a less useful test and values closer to 1 suggests a perfect test. An AUROC of between 0.75 and 1 is widely accepted as an indication of the most useful tests.

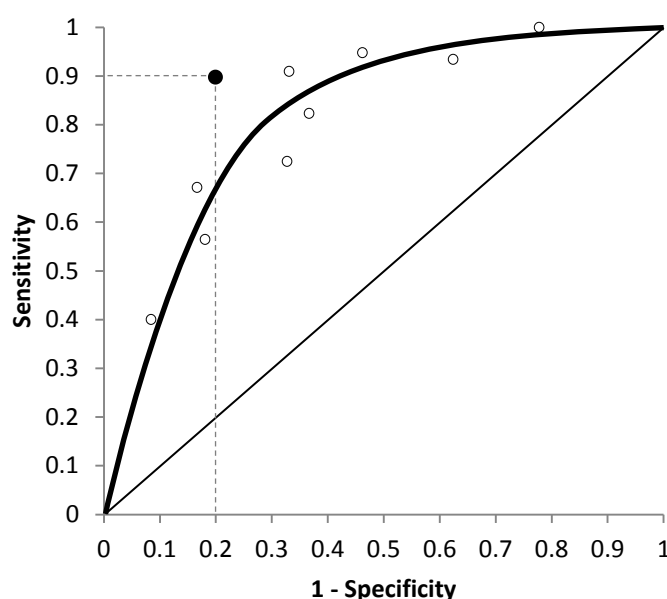


Figure 3 Example of a receiver operator characteristic curve

Table 15 The two by two table

	Number of subjects with target disorder	Number of subjects without target disorder
Number of subjects with positive result	True positives	False positives
Number of subjects with negative result	False negatives	True negatives

Other than sensitivity and specificity, accuracy can also be described using likelihood ratios (LRs).¹⁶⁰⁻¹⁶³ LRs express sensitivity and specificity as one value and essentially give the probability of a test being correct versus the probability of the same test being incorrect. If the parameters of this study are used a positive LR can be defined as the probability of

death within 48 hours occurring as predicted by the Δ variable value (positive test) versus the probability of surviving beyond 48 hours when death was predicted by the same Δ variable value (positive test). As described in the paper, a Δ RR of 8 bpm or higher has a 3.4 times greater likelihood of predicting 48 hour mortality than survival. A negative LR is simply the reverse; the ratio between a negative test predicting survival versus death. LRs are calculated from the sensitivity and specificity of a test which in turn is calculated using a two by two table (Table 15).

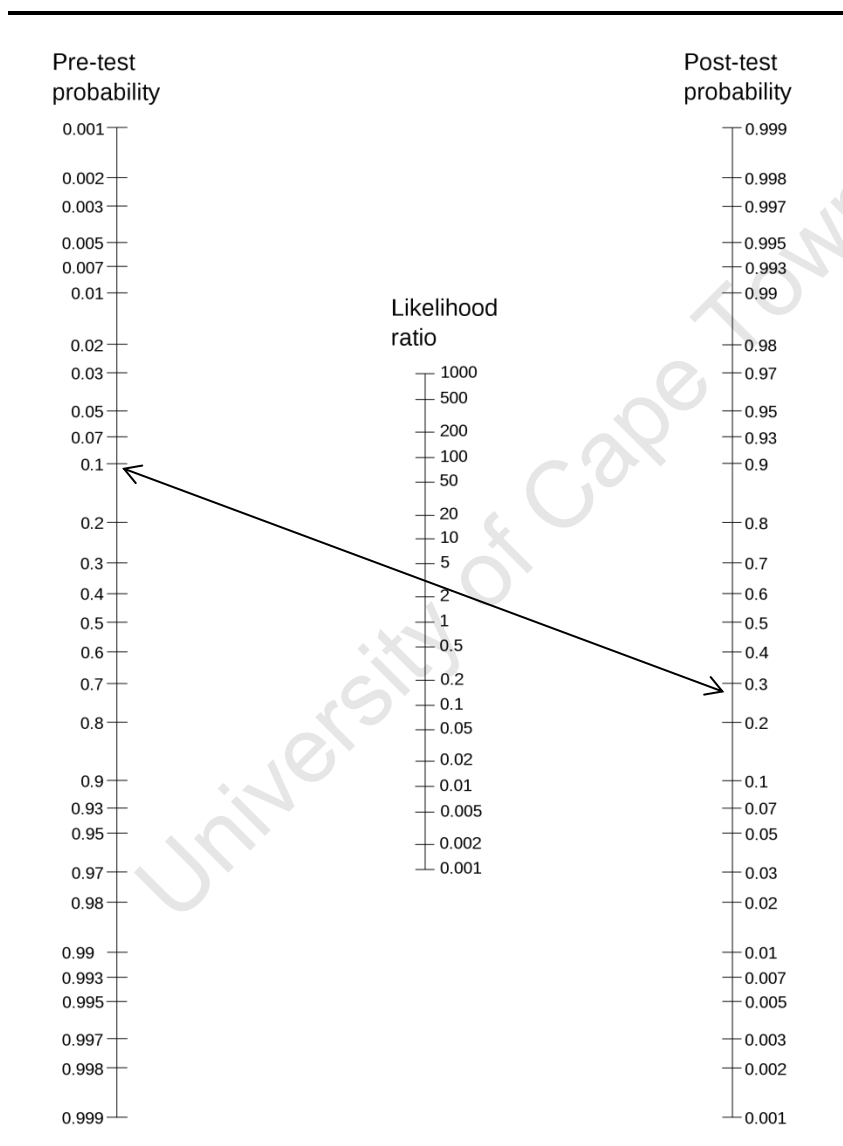


Figure 4 Fagan nomogram

Sensitivity is calculated as the number of true positives divided by all subjects with the target disorder and specificity as the number of true negatives divided by the number of all subjects without the target disorder. The positive LR is calculated as sensitivity divided by [one minus specificity] and the negative LR as [one minus sensitivity] divided by specificity.

A positive LR greater than 1 rules-in disease if the test is positive and a negative LR less than 1 rules-out disease if the test is negative. LRs can be used to calculate the post-test probability of a disease. In order to do this a Fagan nomogram (**Figure 4**) and the pre-test probability are required. By drawing a straight line on the Fagan nomogram from the pre-test probability through the LR the post-test probability can be found where the line crosses the third axis (i.e. a pre-test probability of 10% with a LR of 3.4 would result in a post-test probability of 28%, see **Figure 4**). Most positive LRs range between two and thirty with the majority of tests (laboratory tests and imaging) scoring positive LRs under ten, whilst positive LRs for history and assessment tend to be similar or better.¹⁶⁴ As an example the positive LR of blunt intra-abdominal injury ruled in by the clinical finding of a seatbelt sign is nearly ten, whilst that of an abnormal pelvic x-ray is only 1.6.¹⁶⁵ The most useful positive LRs tend to be closer to ten. It is important to note that LRs are not linear, meaning that the power of a positive LR of fifty is not ten times that of a positive LR of five.^{162,163} The closer a LR is to one (whether positive or negative) the less useful it becomes.

Table 16 Negative likelihood ratios at cut points nearest to 95% specificity

Variable	Cut point	Negative LR	95% CI
Δ RR	8	0.87	0.8-0.95
Δ SI	0.2	0.9	0.83-0.97
Δ SBP*	-37	0.95	0.89-1.01
Δ HR	21	0.98	0.92-1.03

CI, confidence interval; LR, likelihood ratio; RR, respiratory rate; SI, shock index; SBP, systolic blood pressure; HR, heart rate; *, reducing value will increase specificity

Results

The interesting thing about the accuracy statistics of this study is the weak sensitivity results. The implication of this is that the Δ variables' negative LRs are all very close to 1, suggesting that although some of the Δ variables have reasonable rule-in value, their rule-out value for 48 hour mortality is negligible and should not be used for this purpose. Error! Reference source not found. gives the negative LRs for cut points nearest to 95% specificity. The best negative LR was for Δ RR (0.87) which is rather unremarkable finding. It is not known whether increasing the sample size to include CNS injury and prehospital intubated patients would improve accuracy and this should be considered in future research proposals. Mortality rates associated with absolute differences as reported by both Arbabi

and Franklin were mentioned in the paper. According to their findings an absolute decrease in SBP from prehospital to ED resulted, on average, in an approximately 2.5 times higher mortality.^{117, 118} When a similar statistical approach was applied to this study's data set a 1.3 times higher 48 hour mortality resulted. Arguably, excluding CNS injury from this study's sample would have accounted for this finding. However, the exclusion of CNS injury would suggest that the remaining causes of death (mainly haemorrhagic) were at least somewhat represented by absolute changes in vital signs. For the other vital signs an absolute increase in RR and SI from prehospital to ED were associated with a 1.4 and 1.2 times increase in 48 hour mortality respectively, whilst an increase in HR made no difference at all.

The weak value of Δ HR as a predictor of 48 hour mortality was an unexpected finding. Despite an increase of HR of more than 20BPM from prehospital to ED having a specificity of 95%, the negative findings were relentless: none of its AUROC results were significant, suggesting that the Δ variable's ability to correctly rank a patient's probability of dying within 48 hours was no more likely than ranking the probability of surviving. In addition, both positive and negative LRs were very close to one (with 95% confidence intervals in fact crossing one). It is unclear why Δ HR did not perform better. One suggestion was that perhaps the relative bradycardia phenomenon (as defined in **Chapter 1**) had been responsible. From the sample 1628 prehospital cases and 414 ED cases could be defined as relative bradycardic (6% and 1.5% of the full sample respectively). Only four patients with a prehospital relative bradycardia died. None of these deaths included patients where the HR increased by more than 20BPM when measured in the ED. However, ten deaths, 9% of all deaths in the sample, were associated with a relative bradycardia in the ED, resulting in a mortality rate of 2.4% which is 6 times higher than that of the overall mortality rate. Although interesting, this study was not set up to evaluate the phenomenon of relative bradycardia. The numbers described here are small and may not have sufficient power to make any deductions. Formal statistical analysis were therefore not undertaken to evaluate this finding any further, although this clearly warrants future study.

AUROC results were disappointing overall with not a single result achieving an AUROC greater than 0.75 (not even when considering their confidence intervals). This finding suggests that these Δ variables are not really useful to predict 48 hour mortality and likely has very little clinical utility. As with accuracy, increasing the sample to include CNS injury and prehospital intubated patients might result in a different finding. However, since many

of the patients with CNS injury associated with a poor outcome will already have a clinical feature which can be easily calculated at the bedside (low GCS), the value of adding Δ variables would likely be marginal.¹⁵⁴ Further study would be required to evaluate this specifically.

Limitations

As mentioned above, this sample did not include CNS injury or patients that were intubated prehospital. Cannon, Arbabi or Franklin did not specifically exclude these cases.^{110,117,118} As described in the paper, these exclusion criteria were used to ensure that injuries that could affect vital signs without any significant contribution from haemorrhage were largely excluded. It is possible that Cannon, Arbabi and Franklin's findings were exclusively due to CNS injury as this differentiation is not clear from these papers. Given Arbabi and Franklin's finding of a mortality association with an absolute decreased SBP from prehospital to ED and this study's finding of a highly significant AUROC for Δ SBP for 48 hour mortality for the full sample, it is further possible that Δ SBP might be the best predictor for 48 hour mortality for all-cause trauma. To test these hypotheses further research would be required. Additional limitations were discussed in the paper.

Chapter conclusion

The difference between vital signs measured prehospital and in the ED for patients without CNS-injury has some value in predicting 48 hour outcome, although the accuracy is not very good. Of all the Δ variables, Δ SBP and Δ RR performed best overall, whilst Δ SI performed best in the ISS 9-15 subgroup. Unfortunately none of the Δ variables had AUROCs greater than 0.75 and positive LRs were only marginally better than negative LRs which were quite close to one. Delta RR had the best positive LR and this was for an increase in RR of 8bpm. Arguably all of the Δ variable values were such that given a clinical setting where the prehospital vital signs were known, the sizeable difference is likely to result in a high clinical index of suspicion of injury. It seems unlikely that the astute clinician would ignore a SBP drop of 37mmHg, or an increase of HR and RR by 21BPM and 8bpm respectively in the event of acute trauma and this study proves to a certain extent that it is wise to continue to do so. This study further emphasises the importance of considering prehospital vital signs during triage; i.e. a SBP of 134 mmHg in a patient aged 76

might raise no concerns but if it had dropped 37 mmHg from a value of 171 mmHg (the 75th percentile in a normal population), information about the fall in SBP should influence decision-making. Delta variables should be further investigated making use of samples that include CNS-injury as well as higher penetrating injury prevalence. Consideration should also be given to including a structured assessment of prehospital times, injury-types and treatments offered and how this affected outcome.

University of Cape Town

Chapter 6

Vital signs, shock index and age-based markers as indicators of mortality

Reference

Bruijns SR, Guly HR, Bouamra O, Lecky F, Wallis LA. The value of traditional vital signs, shock index and age-based markers in predicting trauma mortality. J Trauma Acute Care Surg. 2013;74(6):1432-7

Declaration of author

In the case of Chapter 6, the nature and extent contribution to the work was the following:

- **Nature of contribution:** SRB and HRG came up with the original idea; SRB did the majority of planning, wrote the first and subsequent drafts of the proposal, conducted the statistical analysis, wrote the first and subsequent drafts of the manuscript and this chapter and is the corresponding author and guarantor of the publication; HRG and LAW contributed to the proposal, manuscript and chapter; OB contributed to the statistical analysis and manuscript; FL contributed to the planning and manuscript
- **Extent of contribution:** SRB: 75%; HRG: 10%; LAW: 5%; OB: 5%; FL: 5%

The following co-authors contributed to the work

1. Prof Lee A Wallis
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3. Dr. Omar Bouamra
4. Prof. Fiona Lecky

Signed by candidate

Signed: Stevan R Bruijns

Declaration by co-authors

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other author of the publication according these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from date indicated below

Location of stored data: Raw data are stored with the Trauma Audit and Research Network. Manipulated data are stored within a password protected database at Plymouth Hospitals NHS Trust, Plymouth, United Kingdom.

15 July 2013

Prof Lee A. Wallis

Date

15 July 2013

Dr Henry R. Guly

Date

Main findings

- The mathematical combinations of vital signs in relation to each other and age described in **Table 17** are better than vital signs alone in ruling in 48-hour mortality
- Older age is significantly associated with 48-hour mortality (age is used in four of the five equations from **Table 17**).

Argument for conducting study

It has been explained earlier that traditional vital signs, though emphasised as important, have severe limitations in predicting mortality in trauma. Theoretically, this could be due to confounding factors but this thesis has already established the minimal effect of immobilisation, transport and anxiety on traditional vital signs. In Chapter 5 the association of the difference between the ED and prehospital vital signs with 48-hour mortality was evaluated and showed that accuracy remained low despite the dynamic nature of the evaluation. It is important to try to find better markers to predict mortality and this final part of the thesis will look at combining vital signs not just with each other but also with age. As described in **Chapter 1**, previous research has shown that mathematical combinations of vital signs do better at predicting a variety of trauma related outcomes than the individual vital signs.^{8,110-114,166} The SI for instance has been shown to identify mortality, serious injury and massive transfusion need, whilst occult haemorrhage could be identified by the ROPE.^{8,110-114,166} A more recent study looked at combining the SI with age in older patients.²³ The result was an even more specific marker for 48-hour mortality than SI alone. The useful thing about SI, ROPE and SI times age (SIA) is that all of the information needed to do these simple calculations is readily available at the point of care, unlike for instance a blood test or radiograph result.

Age has been shown to be a significant determinant of mortality in trauma. As described in **Chapter 1** older age tends to be associated with higher mortality despite lower severity injury, often normal-appearing vital signs and independent of pre-existing medical conditions.^{24,99,103,105-109} The likely reason for an increased mortality is related to a decrease in the elderly person's capacity to compensate for the acute physiological changes brought about by injury and/ or haemorrhage.^{2,41} A measure of physiological reserve already exists in the form of the maximum HR. Defined as 220 minus age it is commonly used in sports medicine.^{115,116} If maximum HR is able to describe physiological reserve with reasonable

accuracy in different age groups during exercise then perhaps it could do the same in traumatic injury or haemorrhage. It is also possible that as with SIA, use of the maximum HR might be useful in predicting 48-hour mortality. The markers (known and novel) evaluated in this study are all described in **Table 17** below.

Table 17 Calculation of markers evaluated in study

Marker	Definition
Shock index	HR/SBP
Shock index times age (SIA)	HR/SBP x age
Minpulse (MP)	(Maximum HR) –HR
Pulse-max index (PMI)	HR/(maximum HR)
Pressure-age index (BPAI)	SBP/ age

Maximum HR is calculated as 220 minus age.

Aim

To derive markers utilising age and maximum HR in combination with traditional vital signs and to evaluate and contrast these, together with the SI and SIA, with HR, SBP and RR in predicting 48 hour mortality following non-CNS trauma.

Objectives

1. To derive markers utilising age and maximum HR in combination with traditional vital signs
2. To evaluate the relationship of age with 48-hour mortality
3. To evaluate the relationship of HR, SBP and RR with 48-hour mortality
4. To evaluate the relationship of the markers described in **Table 17** with 48-hour mortality
5. To establish the threshold for age, HR, SBP, RR and the markers described in **Table 17** that rules in 48-hour mortality at 90% specificity
6. To establish the threshold for age, HR, SBP, RR and the markers described in **Table 17** that rules in 48-hour mortality at 95% specificity

A copy of the published paper follows on the next six pages

Copy of published paper

The value of traditional vital signs, shock index, and age-based markers in predicting trauma mortality

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BACKGROUND:	Systolic blood pressure (SBP), heart rate (HR), and respiratory rate are poor predictors of trauma outcome. We postulate that HR/SBP (shock index [SI]) and novel new markers $SI \times \text{age}$ (SIA), SBP / age (BPAI), maximum HR $(220 - \text{age}) - HR$ (minpulse [MP]), and $HR / \text{maximum HR}$ (pulse max index [PMI]) are better predictors of 48-hour mortality compared with traditional vital signs.
METHODS:	Data were extracted from the Trauma Audit and Research Network database. Exclusions included any head or spine injury and prehospital intubation or cardiac arrest. Area under receiver operator characteristic curve (AUROC) was determined for 48-hour mortality for all variables and age. A threshold for each marker was derived using the specificity (rule-in) cutoffs at both 90% and 95% from the receiver operator characteristic curve. Positive likelihood ratios were described for each marker's derived threshold.
RESULTS:	Vital signs, markers, and age were all significantly associated with 48-hour mortality ($p < 0.001$). HR, SBP, and respiratory rate fared worst overall (AUROC = 0.69, 0.66, and 0.66, respectively). SIA, MP, PMI, BPAI, and SI were significantly ($p < 0.05$) better than age at predicting 48-hour mortality (AUROC = 0.79, 0.77, 0.77, 0.74, 0.73, and 0.68, respectively; AUROC for age = 0.68). Thresholds derived for these five markers were values 55 or greater, 44 or less, 70% or greater, 1.5 or less, and 0.9 or greater, respectively, each with a specificity of 95% for 48-hour mortality (positive likelihood ratios were 8.4, 6.1, 6.7, 6.6, and 7.5, respectively). The likelihood of death in 48 hours was 8.4 times more likely if SIA was greater than 55 than if it was lower.
CONCLUSION:	Older age seems to be significantly associated with early mortality. Newer markers, especially those combining traditional vital signs with age (SIA, BPAI, MP, and PMI), may contribute to better trauma triage of patients with blunt injuries than traditional vital signs. (<i>J Trauma Acute Care Surg.</i> 2013;74: 1432–1437. Copyright © 2013 by Lippincott Williams & Wilkins)
LEVEL OF EVIDENCE:	Prognostic/epidemiologic study, level III.
KEY WORDS:	Vital signs; emergency treatment; advanced trauma life support care; sensitivity and specificity; mortality.

The vital signs of blood pressure, heart rate (HR), and respiratory rate (RR) have traditionally been used to inform trauma team activation and trauma management,^{1,2} although the value of these signs and their reference ranges have been disputed.^{3–8} Newer markers such as the shock index (SI) and HR over pulse pressure evaluation index (ROPE) have aimed to improve the predictive value of vital signs through using combinations of the traditional signs with some success.^{7,9–13} ROPE has been shown to identify occult hemorrhage,^{12,13} and SI has been used to identify mortality and the need for massive transfusion and as a marker for significant injury when HR and blood pressure are normal.^{9,11,14}

The elderly pose a particular difficulty in the interpretation of both the traditional vital signs and the SI. Older persons tend to have less sympathetic-responsive HRs and higher systolic blood pressures (SBP).^{15,16} This results in an increase in false-negative values (even for SI) as age increases. In an attempt to compensate for this problem, Zarzaar et al.¹⁷ proposed a modification to the SI by multiplying it with the patient's age (SIA); this performed better than either traditional vital signs or SI in the group older than 55 years. Their results have not yet been reproduced.

Maximum HR is the ceiling for HR during physical exertion, and it is known that this decreases with age.^{18,19} The maximum HR is usually defined as $(220 - \text{age})$.^{18,19} For an individual, this must be an approximation, but it has been used when prescribing exercise programs, as a criterion for achieving maximal exertion and as a clinical guide during diagnostic exercise testing.^{18,19} Simply put, based on the maximum HR, an average 20-year-old should tolerate an HR of 100 beats per minute (50% of maximum HR) with greater ease than an octogenarian would (71% of maximum HR). Although commonly used in sports physiology,^{18,19} no literature could be found to show that maximum HR had ever been used in the trauma setting. We postulated that if maximum HR describes a person's ability to respond to the physical stress of exercise, it might also indicate their ability to adapt to the stress of trauma and that the difference between the maximum HR and the

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actual HR should be a measure of physiological reserve. Two ways of expressing this would be the numeral difference between the maximum HR and the HR, which we called minpulse (MP), and the HR expressed as a proportion of the maximum HR, which we called the pulse max index (PMI).

Another possibility, given that hypertension is more common in the elderly,^{15,16} would be to express the SBP as a function of age. Since mean SBP is expected to increase with age,¹⁶ a drop in SBP relative to the mean SBP expected for a certain age group may perhaps be a more accurate marker of hypovolemia than the absolute SBP on its own. A relative drop in SBP (as seen in patients with preexisting hypertension such as the elderly)¹⁶ may go unnoticed if the SBP is considered in isolation (i.e., a relative drop from 160 mm Hg to 140 mm Hg with only the latter SBP considered), but in the context of a patient's age, this drop may become clearer. We devised such an index which we called the blood pressure–age index (BPAI). Since the authors were interested in simple solutions that could be applied in a busy clinical environment, BPAI was simply calculated as SBP over age.

We hypothesized that these markers (MP, PMI, SIA, and BPAI) would be better predictors of physiologic status than either the SBP or HR and thus would predict mortality better than traditional vital signs. The aim of this study was to evaluate the value of traditional vital signs, SI, MP, PMI, SIA, and BPAI, in predicting 48-hour mortality. The objectives were to establish how age, vital signs, and these markers relate to 48-hour mortality and to establish a threshold for age and each of the vital signs and markers that can be used to rule in 48-hour mortality.

PATIENTS AND METHODS

A retrospective observational study was performed using data obtained from the Trauma Audit and Research Network (TARN). Established in 1989 as the UK Major Trauma Outcome Study,²⁰ TARN has its origins in a collaborative project with Howard Champion at the Washington Hospital Center (a statistically based trauma audit was introduced here in the early 1980s). Approximately half of all trauma receiving hospitals in England and Wales currently submit information to TARN (<https://www.tarn.ac.uk/>). This study was approved by the research ethics committee of the University of Cape Town (reference 014/2010) and is reported in accordance with the guidelines set by the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement.

Data from approximately 72,000 subjects older than 16 years were collected from TARN's database for the period 1996 to 2006. Vital signs included in this database are the first recorded after the patient's arrival at the emergency department (within 15 minutes), although exact timings may vary slightly between institutions. Exclusion criteria were head or spinal injuries other than minor; unknown injuries, or patients that required either prehospital intubation or cardiopulmonary resuscitation. Minor head or spine injuries were described as injuries with an Abbreviated Injury Scale (AIS) score of less than or equal to one.²¹ Head and spinal injuries were excluded specifically owing to the influence these may have on vital signs in the absence of hemodynamic compromise.¹

The main outcome was 48-hour mortality. The study variables included traditional vital signs (SBP, HR, and RR), the SI, and new markers, MP, PMI, SIA, and BPAI, of which the equations are described in Table 1. These included both maximum HR–derived functions, MP and PMI, and simple age-derived ones, SIA and the BPAI. Of these, MP, PMI, and BPAI have not been described previously. The ROPE index was not assessed as TARN does not collect data on pulse pressure. The maximum HR used in MP and PMI was calculated as 220 minus age.^{18,19} More recent research has suggested that the true equation for maximum HR may be closer to 208 minus (0.7 times age), although both this and the equation used for this study seem to correlate well between the ages of 30 years and 50 years.¹⁸ To keep equations simple enough for clinical use, it was felt appropriate to use the simpler, more widely used calculation (220 – age).

Inspection of the sample revealed illegitimate outliers for age, SBP, HR, and RR (example, HR of 1 beat per minute (outlier), with SBP of 181 mm Hg and Injury Severity Score [ISS] of 9), which was confirmed using *z* scores.^{22,23} Despite the potential for bias likely to be small given the small proportion of outliers involved, it was felt that since illegitimate outliers were identified, it should be removed before the analysis.

Data analysis was performed using SPSS version 19 (IBM SPSS Statistics for Windows, Version 19.0, IBM Corp., Armonk, NY). Since data were not normally distributed, median and interquartile ranges were used to describe age, vital signs, and markers. Sex and injury severity were also described. An ISS of 9 to 15 was used to describe moderate injury, and an ISS of greater than 15 was used to describe severe injury. The sample was described in terms of the full sample and for outcome at 48 hours (survival or death). A Mann-Whitney U-test was performed (two tailed) to compare the difference between those who were alive or dead at 48 hours. A Spearman's ρ was performed (two tailed) to determine the correlation between age and the markers that included age in its equation. The accuracy of variables was assessed using area under receiver operating characteristic curve (AUROC) for the full sample as well as for moderate (ISS, 9–15) and severe (ISS > 15) injury severity using 48-hour mortality as the main determinant. The AUROC for age was then statistically compared with the AUROC of each marker for the full sample, moderate, and severe injury, respectively, using the method described by DeLong et al.²⁴ To avoid spurious significance being imputed through multiple analyses of the same data, an $\alpha < 0.05$ was regarded as significant throughout for all comparative analyses, and 95% confidence limits were given for likelihood ratios (LRs).

TABLE 1. Markers to be Evaluated

Marker	Definition
SI	HR / SBP
SIA	HR / SBP \times age
MP	Maximum HR – HR
PMI	HR / maximum HR
BPAI	SBP / age

Maximum HR is calculated as 220 – age.

TABLE 2. Outliers With *z* Score Greater Than 3

	n	Percentage
Initial sample	71,882	
Outliers (<i>z</i> > 3)	2,515	3.5
RR	1,223	1.7
HR	859	1.2
SBP	690	1.0
Age	1	0
Final sample	69,367	96.5

Threshold values with a specificity of both 90% and 95% were then described for each marker by using the respective cutoff points from the AUROC. A high specificity cutoff was used because it was considered of greater use in the acute trauma setting to be able to predict death at 48 hours rather than to rule it out. In the same way, the threshold for defining a tachycardia is known to be an HR greater than 100 beats per minute, the two thresholds derived for each marker (using a 90% and 95% specificity cutoff from the AUROC) would each describe a higher likelihood of death at 48 hours when crossed. Corresponding sensitivity and positive LR were calculated for each marker's threshold value.

RESULTS

Table 2 describes the removal of outliers and how the final sample was derived. Just more than half of the sample was male (56%), with a low prevalence of penetrating injury (3%). Unsurprisingly, mortality was highest in the severe injury group (4.6%), and around 58% of all deaths occurred in patients with an ISS greater than 15. Mortality at 48 hours was significantly associated with age, vital signs, and all other markers ($p < 0.001$). There was a 23-year difference between

the median ages of those who died and survived. These findings are described in Table 3. Correlation between age and markers that include age in their calculation was significant ($p < 0.001$; $r = -0.91, 0.84, -0.78$, and 0.48 for BPAI, SIA, MP, and PMI, respectively).

AUROC revealed a highly significant relationship between age and 48-hour mortality (area, 0.68; $p < 0.001$). This relationship was highest in the moderate severity group (area, 0.83; $p < 0.001$). Overall, the AUROC for all vital signs and markers was statistically significant, although markers that included age as part of their calculation had the highest AUROC values. The exception was SI, which does not contain age in its calculation but was still one of the top five markers. Overall, the AUROC values for BPAI, SIA, MP, PMI, and SI were significantly higher ($p < 0.05$) than that of age, not so in the moderate injury group where no significant AUROC difference was found between age and any of the markers. In the severe injury group, only SIA and MP had significantly higher AUROCs than age. These results are described in Table 4.

The SIA thresholds achieved the best positive LR at both 90% and 95% specificity cutoff points (Table 5). The top five markers ranked according to their positive LR were SIA, SI, PMI, BPAI, and MP, which was similar to the top five AUROC values described in Table 4 (although ranked differently). The traditional vital signs, SBP, HR, and RR ranked lower, with age ranking lowest.

DISCUSSION

Emergency physicians and trauma surgeons place a high value on the use of traditional vital signs (SBP, HR, and RR) during trauma team activation and resuscitation,^{1,2,25} despite numerous articles questioning the utility thereof.^{3–8} Given the relative ease with which these markers can be obtained at the bedside during assessment, it is not difficult to see why they are

TABLE 3. Descriptive Statistics

	All		Outcome in 48 h			
			Survival		Death	
n (% of all)	69,367		69,102 (99.6)		265 (0.4)	
Male, n (%)	38,948 (56)		38,805 (99.6)		143 (0.4)	
ISS = 9–15, n (%)	32,154 (46.4)		32,076 (99.8)		78 (0.2)	
ISS > 15, n (%)	3,350 (4.8)		3,196 (95.4)		154 (4.6)	
Penetrating, n (%)	1,962 (3)		1,943 (99)		19 (1)	
	Median	IQR	Median	IQR	Median	IQR
Age, y	49	32–67	49	32–67	72	46–82
SBP, mm Hg	136	120–152	136	120–152	120	91–145
HR, beats/min	80	72–92	80	72–92	98	80–115
RR, breaths/min	18	16–20	18	16–20	20	18–28
SI	0.6	0.5–0.7	0.6	0.5–0.7	0.8	0.6–1.1
SIA	29	20–38	29	20–38	51	34–65
MP	88	70–106	88	70–106	59	41–77
PMI	50%	0.4–0.6	50%	0.4–0.6	60%	0.5–0.7
BPAI	2.8	2.1–4.2	2.8	2.1–4.2	1.8	1.4–2.7

Associations for age, vital signs, and markers between the two outcomes were all significant at $p < 0.001$ (Mann-Whitney U-test).

IQR, interquartile range.

TABLE 4. AUROC for 48-Hour Mortality (Ranked From Highest to Lowest Area, Age Excluded)

	All			Moderate (ISS = 9–15)			Severe (ISS >15)		
	Area	p	95% CI	Area	p	95% CI	Area	p	95% CI
Age	0.68	<0.001	0.65–0.72	0.83	<0.001	0.78–0.87	0.66	<0.001	0.61–0.71
SIA	0.79*	<0.001	0.76–0.82	0.85	<0.001	0.80–0.90	0.74*	<0.001	0.70–0.78
MP	0.77*	<0.001	0.74–0.80	0.82	<0.001	0.77–0.87	0.73*	<0.001	0.68–0.77
PMI	0.77*	<0.001	0.73–0.80	0.77	<0.001	0.71–0.83	0.71	<0.001	0.66–0.75
BPAI	0.74*	<0.001	0.71–0.78	0.83	<0.001	0.78–0.88	0.71	<0.001	0.66–0.75
SI	0.73*	<0.001	0.70–0.77	0.65	<0.001	0.58–0.72	0.69	<0.001	0.64–0.73
HR	0.69	<0.001	0.65–0.73	0.61	<0.001	0.54–0.68	0.64	<0.001	0.59–0.69
SBP	0.66	<0.001	0.62–0.70	0.59	0.01	0.51–0.66	0.65	<0.001	0.60–0.70
RR	0.66	<0.001	0.62–0.70	0.59	0.01	0.52–0.65	0.57	<0.001	0.52–0.62

*Area significantly higher than that of age ($p < 0.05$, evaluated using the method of DeLong et al.²⁴).
CI, confidence interval.

used, despite the lack of evidence. However, all the markers tested (SI, SIA, MP, PMI, and BPAI) were more strongly associated with 48-hour mortality than any of these traditional vital signs.

Four of these markers include age in their equation, which demonstrates that age adds meaningfully to the effect already seen with traditional vital signs (Table 4). All four correlated significantly with age, although each of these markers showed a significantly stronger overall association with 48-hour mortality than did age by itself. The question of defining an age beyond which mortality risk starts to increase has been much debated in the literature and ranges from 55 years to 75 years.^{17,26–28} In one study, it was shown that death from

hemorrhagic shock increased from age 75 years, while the risk of death from multiorgan failure increased from age 56 years.²⁶ Whatever the exact age may be, there is widespread agreement that an elderly trauma patient has an increased mortality risk even when less severely injured.^{17,26–32} Table 4 demonstrates this clearly, showing that age contributes substantially to mortality in patients, particularly in those with moderate injuries. It is therefore no surprise that some recommend older age to be included in trauma team activation criteria.³³ Poor trauma outcomes thus seem to be an additional health burden to add to the list of health concerns brought about by an aging population.³⁴ Finding innovative ways of identifying the associated trauma mortality risk is therefore important. It should

TABLE 5. Marker Thresholds at Cutoff Points for Both 90% and 95% Specificity

Marker	Threshold	Specificity	95% CI	Sensitivity	95% CI	+LR	95% CI
90% specificity cutoff thresholds (or nearest; variables ranked from highest to lowest +LR)							
SIA	≥48	90.0	89.7–90.2	55.1	48.9–61.2	5.5	4.9–6.1
BPAI	≤1.7	90.0	89.8–90.3	46.4	40.3–52.6	4.7	4.1–5.3
PMI	≥60%	90.0	89.7–90.2	46.0	40.0–52.2	4.6	4.0–5.2
SI	≥0.8	90.0	89.8–90.2	45.3	39.2–51.5	4.5	4.0–5.2
MP	≤54	90.0	89.8–90.2	43.0	37.0–49.2	4.3	3.7–5.0
HR	≥104 beats/min	89.6	89.4–89.9	41.1	35.2–47.3	4.0	3.4–4.6
SBP	≤110 mm Hg	89.8	89.6–90.0	36.6	30.9–42.7	3.6	3.1–4.2
RR	≥24 breaths/min	87.8	87.6–88.1	39.6	33.7–45.8	3.3	2.8–3.8
Age	≥81 y	90.0	89.8–90.2	30.2	24.8–36.2	3.0	2.5–3.6
95% specificity cutoff thresholds (or nearest; variables ranked from highest to lowest +LR)							
SIA	≥55	95.0	94.8–95.1	42.3	36.3–48.5	8.4	7.2–9.7
SI	≥0.9	95.0	94.9–95.2	37.4	31.6–43.5	7.5	6.4–8.8
PMI	≥70%	95.0	94.8–95.1	34.0	28.3–40.1	6.7	5.7–8.0
BPAI	≤1.5	95.0	94.8–95.1	33.2	27.6–39.3	6.6	5.6–7.9
MP	≤44	94.9	94.8–95.1	30.9	25.5–36.9	6.1	5.1–7.3
RR	≥27 breaths/min	95.3	95.1–95.4	25.7	20.6–31.4	5.4	4.4–6.7
HR	≥112 beats/min d	95.0	94.8–95.1	27.2	22.0–33.0	5.4	4.4–6.6
SBP	≤101 mm Hg	94.1	93.9–94.2	31.3	25.9–37.3	5.3	4.4–6.3
Age	≥86 y	95.0	94.8–95.1	17.4	13.1–22.6	3.4	2.6–5.5

CI, confidence interval.

be noted that the presence of preexisting medical conditions in trauma patients has a similar effect, and this is in addition to but independent of older age.³⁵

SIA, which combines SBP, HR, and age into one marker, performed best overall. It had a positive LR of 8.4, meaning that the likelihood of death at 48 hours is 8.4 times more likely if the SIA is greater than the threshold value of 55 than if it is lower. Zarzaar et al.¹⁷ previously described an SIA threshold greater than 39.3 predicting a higher risk of 48-hour mortality, but this was for a specificity of 81%, whereas our specificity was 95% (their sensitivity and positive LR were 45% and 2.4, respectively). Population differences almost certainly played a role. The novel maximum HR markers PMI and MP showed good associations with 48-hour mortality. A PMI greater than 70% would suggest that 48-hour mortality is 6.7 times more likely than if it was less than 70% and an MP less than 44 would suggest 48-hour mortality 6.1 times more likely than if it was more than 44. SI was the only marker that performed well but did not include age in its equation. A threshold of 0.9 (with a positive LR of 7.1) corresponded with what is described in the literature.^{7,9,14,17}

Although it is not difficult to calculate any of these markers, it is certainly more cumbersome than obtaining traditional vital signs. However, once these results have been validated, ease of use can be greatly improved by incorporating these markers' calculations in existing smartphone or handheld device applications. Alternatively, overhead monitoring devices could also be programmed to automatically calculate these markers from the measured traditional vital signs and then display it in real time.

This study has several limitations. It is not clear from these data how the markers may relate to a population where penetrating trauma is more prevalent. SIA has been evaluated previously but only in a blunt injury population.¹⁷ So far, no marker with age as part of its calculation has been evaluated in a penetrating injury cohort and the markers MP, PMI, and BPAI have been described here for the first time. Since patients with penetrating injury tend to be younger,³⁶ the thresholds for markers that include age may be affected. The exclusion criteria for this study required the removal of all data sets of patients with central nervous system (CNS) injury. As the inclusion of a CNS injury is more likely to result in death than any other type of injury,³⁷ the mortality rate in this sample was found to be lower than expected. TARN data that include CNS injury show a 30-day mortality rate of 18% when head injury is present, compared with 3.5% when it is not.³⁷ It should also be considered that only one set of vital signs was recorded in the TARN database and that preceding or subsequent measurements may have differed.

In conclusion, when dealing with the acutely injured elderly patient, practitioners must remain vigilant as age is a significant indicator of mortality—especially in those with moderate injuries. Newer markers, especially those combining vital signs with age, may contribute to better triage of patients with blunt injuries than currently used traditional vital signs would. This was a derivation study, and these findings should be validated either prospectively or against data from another large database. Further study is required to establish whether any of these markers will remain effective in a sample that

includes head or spinal injury, a higher penetrating injury cohort, or a sample with a high mortality rate among younger trauma patients.

AUTHORSHIP

S.R.B. is the guarantor of this article and was responsible for the bulk of the planning, conduct, and reporting. S.R.B. reviewed the literature and wrote the first draft. All authors participated in the study design, data interpretation, and article preparation.

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DISCLOSURE

We wish to confirm that there are no known conflicts of interest associated with this publication, specifically no pharmaceutical or industry support that could have influenced its outcome.

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Discussion of study

Methods

The equation used to derive maximum HR is in fact not the best representation of maximum HR (as alluded to in the paper). It is however the easiest equation to calculate without the use of additional adjuncts.^{115,116} The more accepted (although not widely used) equation is 208 minus (0.7 times age).¹¹⁵ When compared, the 220 minus age equation overestimates maximum HR in younger adults and underestimates it in older adults.¹¹⁵ An intersection point could be found at around age 40 years with good correlation between the ages of 30 to 50 years.¹¹⁵ The standard deviation (SD) varied approximately 10BPM from that of the more scientific calculation, notably at the extremes of age.¹¹⁵ The main reason why maximum HR is important to cardiologists and sports physiologists is that it can be used to calculate the HR reserve (maximum HR minus resting HR) which in turn serves as a proxy for VO_2 (VO_2 is the capacity of a subject's body to process oxygen during exercise).^{116,167} Both maximum HR and VO_2 can be measured through physiological tests but this is cumbersome in practice and seldom used unless accurate values are absolutely required.¹¹⁶ For everyone else it simply gets calculated using one of the equations mentioned. Despite research showing that 220 minus age is less accurate, it is still favoured, probably because it is easier to calculate and more widely known.¹¹⁶ As the aim of this study was to derive easy to use equations, use of the 208 minus (0.7 times age) equation would simply not be practical. Given the SD above and the fact that that the maximum HR result would either be an under- or overestimation depending on age, it can be inferred that the result (if the 220 minus age equation was used) would differ by about 10BPM in 68% of subjects (one SD) and 20BPM in a further 27% (two SDs). It was agreed that this was not ideal, but that use of a complex equation would be even less practical. In addition, the experimental design of this study allowed some leeway and thus the 220 minus age equation was used to describe maximum HR.

Maximum HR was used as part of two equations in this study (**Table 17**). As described above, calculating the HR reserve is one of the main reasons maximum HR is important.¹¹⁶ It followed that if HR reserve were calculated as being maximum HR minus resting HR, that for this study maximum HR minus the trauma HR from the TARN database should be the most obvious starting point. In contrast to HR reserve this equation proposed to describe what was left of HR reserve. The name for the equation, MinPulse (MP), was simply chosen to describe in brief what was done with the maximum HR and it is foreseeable that in

future publications it might take on a different name. Another use for maximum HR, after calculating HR reserve, is the %HRmax; the proportion between the exercise HR, and the maximum HR.¹⁶⁸ It is this value which is of particular importance to sports physiologists as it is used to predict %VO₂max during exercise, allowing them to direct %VO₂max by controlling the exercise HR within a certain reference range (as calculated using a preset %HRmax).¹⁶⁸ Thus for the purposes of this study exercise HR was simply replaced by trauma HR. The resulting equation, similar to the %HRmax was presented as a percentage (%). Again the name for the equation, Pulse-max Index (PMI), was simply chosen to describe in brief what was done and may change if used in future research. The argument for the Pressure-age Index (BPAI) is made in the paper.

As in **Chapter 5**, outliers were removed from this data sample before analysis commenced using z-scores.¹³² As can be seen from table 1 in the paper, outliers accounted for 3.5% of the initial sample. It was pointed out during statistical peer review that outliers affected only a small number of cases and that the effect for bias was likely to be small. As the vital signs were to be used not just as is, but also in equations with each other and age, it was felt that removal was justified in order to avoid further bias where calculations were concerned. In addition, as mentioned in the paper, it would have been wrong to leave outliers in the sample after these were identified.

As it is already known that increased age is strongly associated with increased mortality in trauma,^{24,103,105-108} it was important to show whether any association between the markers and mortality was just due to their correlation with age or whether the particular combination of vital signs in the equation contributed to this. AUROC statistics were used to show each marker's accuracy in predicting 48-hour outcome, whilst Spearman's Rho was used to see if markers containing age as part of the equation still had a relationship with age (Spearman's Rho is the non-parametric alternative to Pearson's correlation coefficient).¹³² Markers with an AUROC that was similar to, or better than the AUROC for age and correlated closely with age, would be more likely to have gained most of their effect from age, and vice versa for markers that correlated less well given similar AUROC findings. Consequently if age was largely responsible for the accuracy of a particular marker then perhaps it would be easier to simply use age to predict 48-hour outcome and not bother with the calculations at all.

Subgroups were analysed for injury severity to see if markers differed in their accuracy between these. It is already known that age is associated with mortality independent of

injury severity. In particular, the elderly with mild and moderate injuries (ISS<16) have been shown to have a higher mortality than younger subjects with injuries of the same ISS.^{24,109} This effect appears to be less prominent at a higher ISS (ISS>15).^{24,109}

Consequently data were evaluated not only for the whole study sample, but also for two subgroups: those with an ISS greater than 15 (severe injury) and those with an ISS of between 9 and 15 (moderate injury). Subgroup analysis would therefore allow markers to reveal their accuracy in predicting 48-hour mortality in the ISS 9 to 15-subgroup which could then be contrasted with the accuracy of age alone. This point was briefly argued in the paper as well.

Finally as part of the derivation, the AUROCs for age, the vital signs and markers were utilised to establish thresholds for each beyond which 48-hour mortality could be ruled in with a high degree of specificity. This rule-in was evaluated at both 90% and 95% specificity, as high specificity (as opposed to high sensitivity) was considered to be more important in trauma triage and care. In other words, knowing that a poor outcome was more likely was considered more useful than knowing that it is not, as the consequences should the former be incorrect would be more devastating than if the latter was wrong. Focussed assessment with sonography in trauma (FAST) is a good example of a highly specific test used as an adjunct in the trauma primary survey; a positive finding of free fluid is highly suggestive of acute haemorrhage although a negative test finding does not rule this out. The dogma is therefore to keep on looking for pathology until this can be ruled out through definitive tests such as a computed tomograph (CT) or through observation. There is however no place for either in the primary survey and hence the thresholds were selected at the high specificity cut-offs: 90% and 95%. As the AUROCs are presented as tables in which values for each variable could simply be read of at any level of specificity or sensitivity, the thresholds were relatively easy to derive. With this information, the corresponding sensitivity was calculated which allowed calculation of the positive LR of each variable's threshold with regards to 48-hour mortality. The positive LR is the probability of a positive test result making a positive diagnosis divided by the probability of a positive test result and making a negative diagnosis.¹⁶² As an example, a HR of greater than 112BPM has a 5.4 times higher likelihood of being associated with 48-hour mortality than survival. A positive LR of one or less is essentially a test that cannot rule in or rule out the condition tested for. Likewise a value over 10 is considered nearly a perfect rule-in test.^{162,163}

Results

ISS, injury severity score; IQR, interquartile range; ■, age<55; ■, age>54

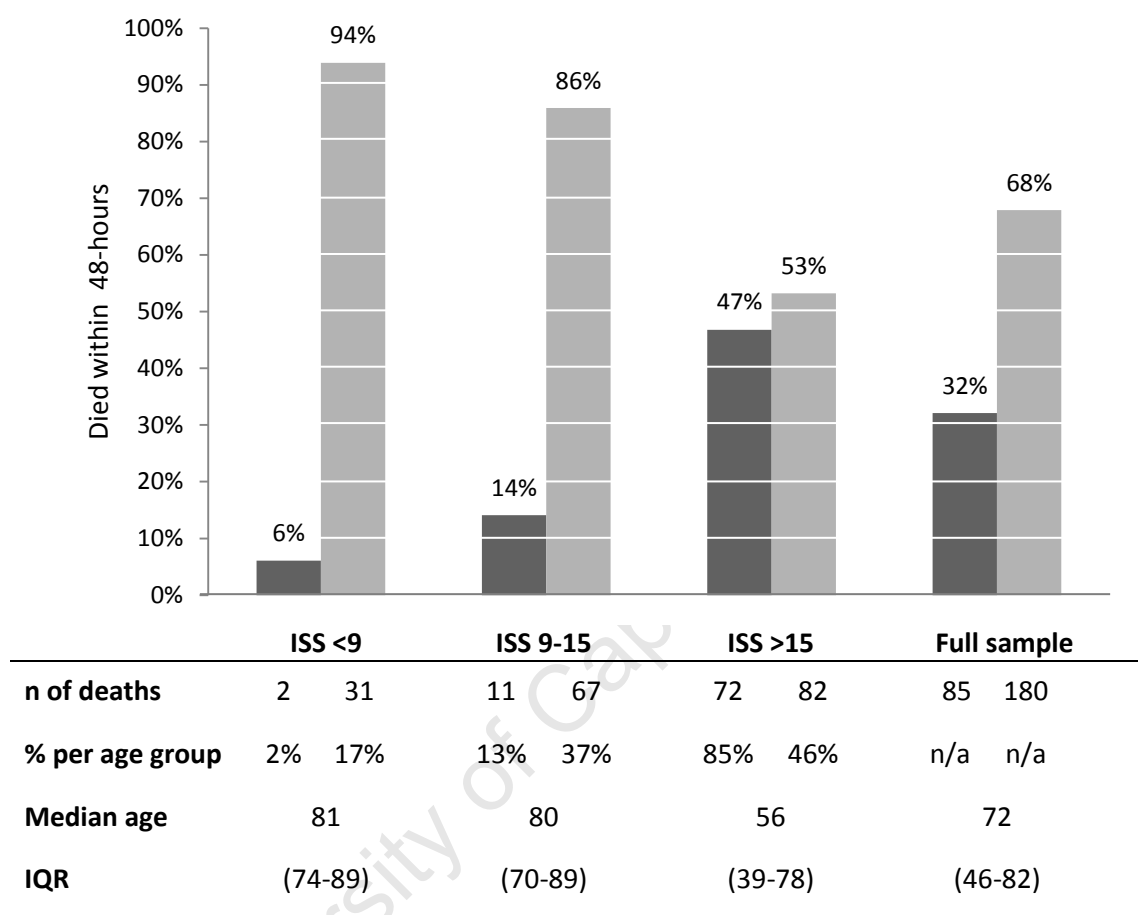


Figure 5 Proportion of subjects that died within 48 hours according to age less, and greater than 55 years per ISS group

It is interesting to note the 23 year median age difference between subjects that survived and died within 48-hours (table 3 in the paper). Additional data (unpublished) show a disproportionately high median age for deaths in the minor to moderate ISS group compared to the severe injury group (**Figure 5**). These findings confirm that the elderly do not tend to cope well with minor to moderate injury in the same way that younger patients do. To produce this table the age cut-off of 55 was used is based on the TRISS age cut-off for older trauma patients.¹⁶⁹ In the **Figure 5's** table, the value: *% per age group* refers to the deaths within a severity and age category as a proportion of deaths in the full sample and the same age category (i.e. for ISS 9-15 and age>54 this would be 67 divided by 180 percent which is 37%).

Table 18 Specificity, sensitivity and positive likelihood ratios for ISS 9-15 subgroup using marker thresholds derived from 95% specificity for the full sample

Marker	Threshold	Specificity	95% CI	Sensitivity	95% CI	+LR	95% CI
SIA	≥55	95.1	94.9-95.4	47.4	36.1-59.0	9.8	7.7-12.4
BPAI	≤1.5	95.6	95.4-95.8	41.0	30.2-52.7	9.4	7.1-12.3
MP	≤44	94.9	94.7-95.2	39.7	29.0-51.5	7.8	5.9-10.3
PMI	≥70%	94.9	94.7-95.2	37.2	26.7-48.9	7.3	5.5-9.8
Age	≥86 years	95.0	94.7-95.2	28.2	18.9-39.7	5.6	3.9-8.0
SI	≥0.9	94.4	94.1-94.7	24.4	15.7-35.6	4.4	2.9-6.5
SBP	≤101 mmHg	94.2	93.9-94.4	19.2	11.5-30.0	3.3	2.1-5.2
HR	≥112 BPM	94.3	94.1-94.6	16.7	9.5-27.2	2.9	1.8-4.9
RR	≥27 bpm	94.7	94.4-94.9	14.1	7.6-24.3	2.6	1.5-4.6

CI, Confidence interval; +LR, Positive likelihood ratio; BPM, Beats per minute; bpm, Breaths per minute

As described in **Chapter 5**, when interpreting AUROC, a value closer to 0.5 suggests a meaningless test (low specificity and sensitivity) and a value closer to 1 suggests a perfect test (high specificity and sensitivity).^{132,159} Subsequently the most useful tests are identified by AUROC values between 0.75 and 1.¹⁵⁹ For the full sample SIA, MP, PMI, BPI and SI's 95% confidence intervals all included 0.75. This was also the case within the two subgroups (moderate and severe ISS) however, with one difference. Age's 95% confidence intervals also included 0.75 in the moderate ISS subgroup. This finding was not shown for either the full sample, or the severe ISS subgroup. In addition it is important to note that age either trumped (or equalled) all of the other markers or vital signs in the moderate ISS subgroup. This finding also links with the findings in **Figure 5** above and strengthens past research that suggests a higher incidence of mortality with increasing age particularly in lower severity groups. If the derived thresholds from the paper are applied to the moderate ISS group, it is found that age's positive LR nearly doubles (**Table 18**) compared to the full sample described in table 5 in the paper. Instead of trailing behind the traditional vital signs, it is now ahead of these, including the SI (**Table 18**). In itself, this finding adds to the growing literature base that supports including age on trauma team activation criteria in order to avoid undertriage and to ensure earlier action are taken to avoid a poor outcome.^{24,103,105-108}

It is important to note that the thresholds derived and given in table 5 in the paper are done so to ensure high specificity (rule-in value). Table 5 also gives the sensitivities for each

which should be seen as a measure of each threshold's rule-out value. Since sensitivity is calculated as the number of true positives divided by the sum of the number of true positives and false negatives, it essentially represents deaths predicted by the threshold as a proportion of the total number of deaths. As an example, SIA therefore predicts 42.3% of all deaths that occurred in the sample, or 112 out of 265 deaths.

Limitations

CNS injury and subjects that were intubated prehospital were not included in this sample and other populations not well represented (including penetrating trauma). CNS injury was a particular exclusion as it is known to confound vital signs by affecting them differently than injury and haemorrhage alone. Cervical lesions may cause spinal shock resulting in hypotension and bradycardia, whilst raised intracranial pressure results in the Cushing's reflex which describes increased BP, a reduction in HR and irregular breathing. CNS-injury accounts for nearly half of deaths from trauma, whilst haemorrhage accounts for only around a third.¹⁷⁰ Median time of death also occurs later for CNS-injury compared to haemorrhage (around 24 hours versus 2 hours).¹⁷⁰ This is likely to be the main reason why 48-hour mortality in this sample was only 0.4% (the 30-day mortality was 1.8% and was not reported in the paper). Arguably, future evaluation of the markers described in this study should include testing in samples that include CNS-injury. Since traditional vital signs are affected differently when CNS-injury is present, it can be expected that the same will apply to these markers. Being aware of the effect of CNS injury on any marker will be important to clinicians dealing with this group of patients and further studies should be done to validate any marker. Given that severe CNS injury often affects mentation, an assessment of the GCS would be a useful marker of severe brain injury and should be included in any such research.

Blunt injury tends to result from road traffic accidents and falls and tends to affect more than one body area. In contrast with blunt injury, penetrating injury affects a specific area which can be isolated or multiple.⁴ It is also more likely to be associated with pure blood loss rather than tissue injury. Mortality for penetrating injury is higher (from 2.5% up to 15%) although blunt injury is more common.^{171,172} Even in our study, penetrating injury mortality was about 2.5 times higher. Since younger patients can be expected to have a higher physiological reserve, the response from vital signs will be different. It is also unclear how this younger population would interact with the markers proposed in this

study which relies significantly on age for accuracy in predicting 48-hour mortality. Further research is required in a population where penetrating injury is more common-place.

Exclusion of prehospital intubated patients certainly had an effect on the incidence of mortality in this study as intubated trauma patients tend to have higher ISS (approximately 26) and mortality rates (approximately 37%) compared to non-intubated patients.¹⁷³ Both values are even higher if the intubation was required prehospital (ISS of approximately 40 and mortality of around 64%).¹⁷⁴ The reason for the exclusion relates to the effects that intubation and the drugs necessary to facilitate this would have on vital signs. Now that a role for the newer markers have been established it would be important to see how these would differ between the intubated and non-intubated patient.

Chapter conclusion

Increasing age is an important predictor of poor outcome within 48-hours. As a result the combination of age and traditional vital signs into the markers presented in this study resulted in markedly better accuracy than the traditional vital signs used to produce them. Given that these markers all require a short calculation, it is arguably not as readily available as reading traditional vital signs from a patient's bedside monitor. However, the much improved accuracy more than makes up for this. It is foreseen that once these markers have been validated in other populations and agreement of thresholds have been established that better ways of acquiring the data will be explored (i.e. incorporating the calculations into handheld devices, smartphones or even the electronic display of bedside monitors).

Conclusion

In trauma, high value is placed on vital signs to guide trauma team activation, triage, resuscitation and further care despite evidence that they are of little value in assessing the volume of blood loss and are poor at predicting outcome.^{4-6,8} This thesis described a number of findings which have not been described previously regarding potential confounders of vital signs in trauma. These include the findings that influences on vital signs from spinal immobilisation, anxiety and transport appear to be negligible or minimal, and that a change in vital signs from prehospital to ED is poorly predictive of early mortality. In addition, vital signs were shown to be unreliable at predicting mortality when within so-called normal reference ranges, and were even unreliable when abnormal. However, it was revealed that by combining vital signs with age, stronger relationships can be formed to predict 48 hour mortality. This included the novel use of measures based on the maximum HR. It is important to consider that a strong argument for less reliance on vital signs in trauma care has already been made in the literature, with more value placed on injury type and mechanism of injury.^{4,17-27} This thesis added to this body of evidence and explored the options for improving the role of vital signs in early trauma prognostication.

As with most research, further areas for study have been identified. The results from this thesis were published in five peer reviewed journals in order to allow other researchers the opportunity to evaluate the findings within their own settings. A summary of the findings which addresses the thesis objectives are presented below.

An evaluation of the physiological effects of conditions that could potentially have an effect on vital signs

Effect of immobilisation

Immobilisation does not seem to have any clinically relevant effect on vital signs in either subjects with no injury (**Chapter 2**) or patients with mild to moderate injury (**Chapter 3**). It was interesting to note during the literature review that very little research exists regarding the relationship between immobilisation and vital signs. A thorough search of the literature was only able to identify a few papers that evaluated the relationship between

immobilisation and the respiratory system and none referring to either SBP or HR.^{86,175-178} Previous research mainly focussed on pain and discomfort caused by different immobilisation techniques and devices.⁸⁶⁻⁹⁰ The studies, described in **Chapters 2 and 3**, appear to be the first describing the effect of immobilisation on vital signs. **Chapter 2** showed that the difference in vital signs following spinal immobilisation in healthy subjects, although statistically significant, is not clinically relevant (**Table 6**): the large increase in discomfort during full immobilisation having only a small effect on vital signs (**Table 8**). In the injured cohort (**Chapter 3**), no clinically relevant difference in either HR or SBP was seen between immobilised and non-immobilised patients (**Table 13**). In addition the effect of immobilisation on vital signs did not vary with age. It could be argued that one of these studies was small and the other was retrospective and therefore do not exclude the possibility that immobilisation might have an effect on vital signs given more serious injury, or even different injury patterns. However, it seems that rejection of the null hypothesis given a severely injured patient cohort is most improbable. The message is simple: if HR, SBP or RR is increased in a spinally immobilised trauma patient, this finding should not simply be attributed to immobilisation without evaluating for pathology first.

Effect of anxiety

Chapter 3 showed that HR and SBP do differ between a non-injured and an injured cohort; this is likely to be caused by anxiety, or injury, or a combination thereof. In **Chapter 3** it was shown that the median HR of a moderately injured cohort was approximately 10BPM higher than that of a non-injured cohort and that this was true irrespective of age (figure 1 A in the paper). As described in the paper, this effect was possibly due to anxiety and a WCE, although injury could have also played a role.^{2,3,70} The study tried to exclude the effect of blood loss by including only uncomplicated, upper extremity and below-knee, lower extremity injury. However, as discussed in **Chapter 1**, the physiological response to injury is a sympathetic response similar to the “fight or flight” response generated by anxiety.^{2,3,71,72} The tachycardia induced by injury is classically described to taper slowly over 14 days from injury;^{3,73} a fairly similar observation made in previously reported research on PTSD in trauma.^{95,138,179} It is questionable whether a clear distinction between anxiety and injury is important or can even be effectively differentiated given the similar physiological pathways. What is important is that an injured and a non-injured population do differ and that this effect is marginal. This study showed that the HR increase remained consistently 10BPM higher in the injured cohort irrespective of age. It is suggested in the paper that as

a result of the injury/anxiety effect, perhaps a different reference range be considered for the HR in injured patients although further research is needed to see if these findings can be replicated in other settings and different injury severity profiles. The SBP difference varied with age with a greater, though clinically irrelevant, difference seen in young adults but no difference in older patients (figure 1 B in the paper). It is likely that the raised SBPs related to injury in children reported previously,¹³⁷ continue into early adulthood, resulting in this paper's findings.

Effect of transport

The study described in **Chapter 4** showed that transport had minimal effect on SBP and HR and this was not clinically relevant. The most interesting finding was that SBP was higher in the ED compared to during transport to the ED contrary to what was expected. Very few studies have looked at the relationship between transport and vital signs with only one having studied the effect in an actual patient group (**Table 4**).^{20-22,96,97} While all of these studies confirmed an increase in adrenergic outflow, only the healthy volunteer studies showed an increase in HR and SBP as well. Interestingly the effect seen in healthy volunteers could be attenuated by administering an anxiolytic suggesting that it is likely to be anxiety causing the reported catecholamine rise.⁹⁷ As it is known that pain has no significant effect on vital signs;⁸²⁻⁸⁵ immobilisation has no clinically relevant effect and patients were specifically selected for the study to exclude haemorrhage and the effects of PMCs and drugs, it follows that any additional effect seen would be due to transport. This effect turned out to not be of much note. The most likely explanation is that in the healthy volunteers' studies, given the absence of injury, vital signs resolved once anxiety resolved; but when injury was present this did not occur. As noted previously, the effect of injury on vital signs are very similar to that of anxiety. However, if the injury remains constant throughout early trauma, then irrespective of whether the injured patient is in an ambulance or the ED, it would be expected that vital signs would also remain constant. It is further implied that age had little effect given that the ED and prehospital vital signs were no different in the two groups despite a significant age difference. This study could not compare the vital signs during transport and in the ED to baseline measurements. However, in **Chapter 3** it was shown that a difference in HR and SBP is measurable between non-injured and injured cohorts. What this study has determined is that from the ED's perspective in a controlled cohort such as this, vital signs measured in the ED do not change much from what was measured during transport.

Novel ways of interpreting vital signs

The value of deteriorating vital signs

Chapter 5 showed that even though deteriorating vital signs can be appropriately specific beyond a predetermined threshold, sensitivity is very low, resulting in disappointing accuracy for predicting 48 hour mortality. Previous research into this is limited to three papers which only evaluated Δ SBP and Δ SI.^{110,117,118} As discussed, inclusion of CNS-injury in these papers would impact on the way the findings are interpreted, as CNS-injury accounts for the largest proportion of trauma mortality.¹⁵³ In the paper described in **Chapter 5**, Δ SBP along with Δ RR scored the best of some very unexciting overall results, whilst Δ SI manages some significant accuracy only when moderate injury severity is concerned (a classification which is usually only made after initial trauma care has been completed). The best sensitivity for any of the Δ variables for a high specificity was but 13%. What was interesting was the low predictive value of Δ HR; AUROC statistics showed that Δ HR was non-predictive of 48 hour mortality irrespective of level of severity, even with a difference of 21BPM or greater between the ED and prehospital measurements. It is possible that the phenomenon of relative bradycardia in trauma (**Chapter 1**) was responsible for this (relative bradycardia in the ED was associated with almost a tenth of all deaths in the sample). It is important to note that data were not weighted for intervention, which is likely the most important reason why the mortality rate was not higher. This study therefore does not advocate that deteriorating vital signs should be ignored given their poor accuracy in predicting 48 hour mortality. It is likely that appropriate intervention as expected from a mature trauma system such as that of the UK curbed mortality which would have affected the findings of this paper. Intervention should therefore continue as directed by current trauma guidelines.⁴ In addition, clinicians would be wise to consider relative hypotension in likely hypertensive populations, such as the elderly. It would however be interesting to compare these findings to that of a cohort where intervention is less aggressive than that of the UK.

The value of combining vital signs with age or other vital signs

Chapter 6 showed that a combination of vital signs is more accurate in predicting 48 hour outcome than a single vital sign on its own. Accuracy improves even further when age is included as part of the combination. In fact age has a nearly similar accuracy of predicting 48 hour mortality to that of HR, SBP and RR (table 4 in the paper, **Chapter 6**). This is likely

due to older trauma patients having an increased mortality, specifically notable in the moderately injured.^{23,24,99,103,105,107,108,180} The use of the maximum HR to calculate trauma HR reserve (MP) and %HRmax (PMI) has not been described before. As markers for predicting 48 hour mortality, both improved accuracy well beyond that of the variables they were made up of (table 4 in the paper). The BPAI was another novel marker introduced in this thesis that showed good accuracy with strong positive LRs to predict 48 hour mortality. Only one marker without age as part of the equation, the SI, improved accuracy. The addition of age to the SI (SIA) improved the SI further although the difference between the two markers was not significant. Both of these markers have been evaluated before with extensive reporting on the SI available in the literature.²³ This study further confirmed what is already known about the relationship between age, trauma and death; older patients have higher mortality than younger patients, particularly with less severe injuries (**Figure 5** and **Table 18**). As a result it would be interesting to see how predictive these markers would be in younger populations.

Further research

Although, the objectives for this thesis were appropriately and thoroughly addressed several areas for further study were brought to light:

1. The main influences on the vital signs in trauma are blood loss and injury. Further study to compare the physiological response to non-traumatic blood loss (e.g. in gastrointestinal haemorrhage) with the physiological response to traumatic blood loss may help to clarify the effects of these two influences. It may also be interesting to determine whether the ATLS haemorrhage classification is useful in the non-trauma haemorrhage setting.
2. The effect of the phenomenon of relative bradycardia on outcome as discussed in **Chapter 5** should be considered for further study.
3. As described in **Chapter 3**, the blood pressure in injured children is higher than the blood pressure of uninjured children of the same age. This difference decreases with increasing age and extends into young adulthood with no difference seen in older adults. The physiology of this process warrants investigation.
4. Measuring anxiety levels in patients with minor to moderate injury and comparing these with vital signs would give more information on the influence of anxiety on vital signs in trauma. It would seem that in the acute setting use of a VAS would be the

simplest way to measure anxiety, although other validated tools exist.¹⁸¹ A prospective design would be required though.

5. Changes in vital signs may be greater with a prolonged prehospital time and this should be investigated with regards to Δ variables. Further research should include study into their applicability in less developed trauma systems with longer prehospital times and in patients with other patterns of injury (such as penetrating trauma and CNS-injury). Perhaps a breakdown of injury by region using the AIS classification could be useful to determine the injury regions which affect Δ variables.
6. As with the SI, the novel markers proposed in this thesis require further validation. This will include validation in younger patients; in patients with CNS injury and in cohorts of patients with undifferentiated injuries including cohorts with a higher proportion of penetrating injury. These novel markers should also be evaluated with respect to their value in predicting outcome and the requirement for a trauma team, intensive care admission and transfusion requirement. The influences of blood loss and trauma on the novel markers could be separated by observing the effect of non-traumatic haemorrhage (e.g. gastrointestinal haemorrhage or blood donors for the effect on low-volume haemorrhage) on the markers. Should these novel markers prove to be more useful than stand-alone vital signs, then they could be used to define a classification of haemorrhagic shock that could replace the current ATLS classification. They might also be considered to augment, perhaps even replace vital signs on standard bedside monitors. The latter would be challenging given that vital signs have been ingrained into the psyche of each medically trained professional (doctors, nurses, prehospital workers and auxiliary staff). However, in more recent years clinicians have become used to seeing additions to monitors, such as an end-tidal CO₂ tracing, and learned how to interpret this. By incorporating these novel markers first into handheld, smart devices, clinicians will get more acquainted with their use before incorporating these elsewhere (such as bedside monitors). This process in itself will require a massive amount of research, likely on an international scale.

When considering vital signs in the trauma setting it is important to consider all the various factors already known that may affect the interpretation thereof. As stand-alone markers, vital signs are not very reliable as predictors of a poor outcome unless fairly deranged; and not at all if within currently accepted reference ranges. Factors, such as immobilisation and transport, have been shown not to influence vital signs to any relevant extent. Even Δ variables may be more reliant on the availability of a developed trauma care environment

and was disappointing in the test setting. Most notable is the novel use of vital signs in combination with other vital signs and/ or age. The difference between the reliability of these and stand-alone vital signs was remarkable. These markers may in future come to replace the current use of traditional vital signs in trauma care.

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Appendices

Appendix A: Patient information sheet

Patient Information Sheet

The Effect of Full Spinal Immobilisation on the Heart Rate, Blood Pressure and Respiratory Rate of Healthy Volunteers (version 4, 06/07/2010, study number: 10/H0203/25)

WE WOULD LIKE TO INVITE YOU TO PARTICIPATE in a research study evaluating the effect of full spinal immobilisation on the heart rate (pulse), blood pressure and breathing (respiratory) rate of healthy uninjured volunteers. We would like to collect this information about you before, during and after fitting full spinal immobilisation. Before you decide we would like you to understand why the research is being done and what it would involve for you. **One of our team will go through the information sheet with you and answer any questions you have.** We'd suggest this should take about 15 to 20 minutes. Talk to others about the study if you wish. The study is part of an educational project in fulfilment of the requirements of a PhD degree through the University of Cape Town, South Africa.

PART 1 (tells you the purpose of this study and what will happen to you if you take part):

THE PURPOSE OF THIS PROJECT is to improve the management of the injured patient by better defining the physiology of the injured patient and to try and identify better ways of identifying blood loss. This study aims to establish whether spinal immobilisation and the manoeuvres commonly used in injured patients (e.g. log roll) affect the heart rate (pulse), blood pressure and breathe rate.

DO I HAVE TO TAKE PART? It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. Withdrawal from the study would not affect your current or future employment (Emergency department staff) or academic progression (Plymouth Medical School students).

WHAT WILL HAPPEN TO ME IF I TAKE PART? You will be asked to rest on an Emergency Department stretcher for 5 minutes whilst your heart rate (or pulse), blood pressure and breathing rate are measured and an assessment is made of your degree of comfort. All of these procedures are routinely performed on patients attending hospitals, primary care centres, etc. They are not painful or invasive and there are no complications. Comfort will be measured by asking you to indicate your experience of comfort or discomfort on a scale from one (no discomfort) to ten (severe discomfort).

This will be followed by a 10 minute period of full spinal immobilisation during which measurements will be repeated. Full spinal immobilisation is a routine procedure used in patients where there is any possibility of a spinal (neck or back) injury. Patients are fitted with a rigid neck brace (cervical collar) and secured on their back to a rigid spinal board with head restraints in order to minimise movement and thereby further injury to the spine. As well as being used on patients, full spinal immobilisation is frequently also performed on healthy individuals during training sessions. Cervical collar, spinal board and head restraints may be uncomfortable for the short time that they are in place, but there are no complications.

The spinal board will then be removed. You will remain on the stretcher for a further 10 minute period of spinal immobilisation (but without the rigid spine board), during which measurements are repeated again

Following this, all spinal immobilisation is removed and you'll be asked to rest a further 5 minutes on the stretcher whilst measurements are repeated for a last time.

EXPENSES AND PAYMENT: You will not be paid to participate in this study.

RISKS INVOLVED IN PARTICIPATION: There are no anticipated risks associated with this study.

BENEFITS INVOLVED IN PARTICIPATION: You will not receive any direct benefit from participation, but the information we get from this study will help improve the treatment of trauma patients.

WHAT IF THERE IS A PROBLEM? Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL? Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Patient Information Sheet (page 2)

The Effect of Full Spinal Immobilisation on the Heart Rate, Blood Pressure and Respiratory Rate of Healthy Volunteers (version 4, 06/07/2010, study number: 10/H0203/25)

END OF PART 1: If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2 (gives you more detailed information about the conduct of the study):

WHAT WILL HAPPEN IF I DO NOT WANT TO WITHDRAW FROM THE STUDY? If you decide to participate, you are free to withdraw your consent regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. If you wish to revoke your consent for the research use, or disclosure of your health information in this study, you must inform the principal researcher.

WHAT IF THERE IS A PROBLEM? If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, you should ask the principal researcher, Dr Stevan R Bruijns. You should contact him at any time if you feel you have been hurt by being a part of this study. His contact details are: Emergency Department, Derriford Hospital, Plymouth, PL6 8DH, UNITED KINGDOM (+44 1752 792505).

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL? Yes. Names on the datasheet will be removed once analysis starts. All data and back-ups thereof will be kept in password protected folders within Plymouth Hospitals NHS Trust's server from where it will be analysed. Raw, unanonymised data will not be transferred outside the UK for either analysis or storage. Processed data may be transferred to associate researchers in South Africa. You should be aware that similar standards of data protection apply under South African law as in the UK. Only the principal researcher will be authorised to use and/or disclose your anonymised health information in connection with this research study. Sometimes the data may need to be looked at by individuals from regulatory authorities. The principal researcher will take all reasonable steps to protect your privacy.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY? The findings will be published as part of a PhD dissertation through the University of Cape Town, South Africa. For your convenience, a summary of the findings will also be made available in both Derriford Emergency Department and the Peninsula Medical School's newsletters. You will not be identifiable in any publication made

WHO IS ORGANISING AND FUNDING THE STUDY? This study is sponsored by Plymouth Hospitals NHS trust (REC reference 10/H0203/25) and funded by the principal researcher. The principal researcher or any of his associates do not receive any remuneration for enrolling you into this study

WHO HAS REVIEWED THIS STUDY? All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC), to protect your interests. This study has been reviewed and given favourable opinion by South West 1 REC. It has also been approved by the Doctoral Degrees Board and REC (reference 014/2010) of the University of Cape Town, South Africa.

FURTHER INFORMATION AND CONTACT DETAILS: Should you wish to have more specific information about this research project information, need advice as to whether you should participate, have any questions, concerns or complaints about this research study, its procedures, risks and benefits, you should speak to the principal researcher, Dr Stevan R Bruijns. You should contact him at any time if you feel you have been hurt by being a part of this study. His contact details are: Emergency Department, Derriford Hospital, Plymouth, PL6 8DH, UNITED KINGDOM (+44 1752 792505). If wish to learn more about research in general please visit the National Research Ethics Service's website: <http://www.nres.npsa.nhs.uk/>

Appendix B: Patient consent form

Centre Number: **Plymouth Hospitals NHS Trust**

Study Number: **10/H0203/25**

Participant Identification Number for this trial

Consent Form

The Effect of Full Spinal Immobilisation on the Heart Rate, Blood Pressure and Respiratory Rate of Healthy Volunteers (Principal researcher: Dr Stevan R. Bruijns)

Please initial the box:

1. I confirm that I have read and understand the information sheet dated 06/07/2010 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my employment, academic progression or legal rights being affected.
3. I understand that data collected during the study, may be looked at by individuals from regulatory authorities. I give permission for these individuals to have access to my data.
4. I agree to take part in the above study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person	Date	Signature taking consent

When completed: 1 for participant and 1 for the researcher site file (consent version 3 06/07/2010)